UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

ORTHOPEDIC AND REHABILITATION DEVICES PANEL

MEETING

FRIDAY, SEPTEMBER 9, 2005

The meeting came to order at 8:30 a.m. in Salons A, B, and C of the Hilton Washington, D.C. North, 620 Perry Parkway, Gaithersburg, MD. Dr. Sanjiv H. Naidu, Acting Panel Chair, presiding.

PRESENT:

SANJIV H. NAIDU, M.D., PH.D.	ACTING PANEL CHAIR
CHOLL W. KIM, M.D., PH.D.	VOTING MEMBER
SALLY A. RUDICEL, M.D.	VOTING MEMBER
FERNANDO DIAZ, M.D., PH.D.	CONSULTANT
MICHAEL J. YASZEMSKI, M.D., PH.D.	CONSULTANT
PAMELA ADAMS, M.S., R.A.F., C.Q.M.	INDUSTRY REP.
CONNIE F. WHITTINGTON, M.S.N., R.N.	CONSUMER REP.
JANET L. SCUDIERO	EXECUTIVE SEC.
MARK MELKERSON, M.S.	FDA

I-N-D-E-X

P-R-O-C-E-E-D-I-N-G-S

8:04 a.m.

MS. SCUDIERO: Good morning. We are ready to begin this meeting of the Orthopedic and Rehabilitation Devices Panel. I am Jan Scudiero, the Executive Secretary of this panel and a reviewer in the Division of General Restorative and Neurological Devices. We have the usual housekeeping first. If you haven't already one so, please sign the attendance sheets that are on the tables by the door and pick up your agenda information.

The next tentatively scheduled meeting of the panel that was tentatively scheduled for November 3rd and 4th is canceled because there is no agenda item ready for panel review.

Upcoming panel meetings are announced on our Advisory Panel website, in the Federal Register, and on the telephone information line. Please monitor

the panel website for future meeting information. Information goes up on this site first before the other two locations.

Finally, as a curtesy to the others in the room please turn off or silence your cell phone during the meeting.

Dr. John Kirkpatrick is unable to be with us today.

I will now read into the record two agency statements prepared for this meeting, the Appointment for Temporary Panel Chair Statement, and the Conflict of Interest Statement.

"I appoint Sandra H. Naidu, M.D., Ph.D., a voting member of the Orthopedic and Rehabilitation Devices Panel as Acting Panel Chair for the September 8th and 9th, 2005, meeting of the panel." This is signed by Daniel G. Schultz, M.D., Director, Center for Devices and Radiological Health on September 7th.

The Conflict of Interest Statement. The Food and Drug Administration is convening today's meeting of the Orthopedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee under

the authority of the Federal Advisory Committee Act of 1972.

The Advisory Panel meeting provides transparency into the agency's deliberative processes. With the exception of the industry representative all members of the panel are special government employees or regular federal employees from other agencies subject to the federal conflict of interest laws and regulations.

FDA has determined that members and consultants of this panel are incompliance with the federal conflict of interest laws including, but not limited to, Part 18 of the U.S. Code, Section 208, and Part 21 of the U.S. Code, Section 355(n)(4).

Under Part 18, U.S. Code, Section 208 applicable to all government agencies, and Part 21 U.S. Code Section 355(n)(4) applicable to FDA Congress has authorized FDA to grant waiver to special government employees who have financial conflicts when it is determined that the agency's need for particular individual services outweighs his or her potential conflict of interest.

Members and consultants who are special government employees at today's meeting have been screened for potential financial conflicts of interest of their own as well as those imputed to them including those of their employer, spouse, or minor child.

These interests may include investments, consulting, expert witness testimony, contracts, grants, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves a discussion on the design of clinical studies for spine devices indicated for the treatment of mild to moderate low-back pain. In accordance with Part 18 U.S. Code Section 208(b)(3) a waiver was granted to Dr. Sally Rudicel.

A copy of the written conflict of interest waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Act, Room 12A30 of the Parklawn Building.

In addition, Ms. Pamela Adams is participating as the industry representative acting on

behalf of all related industry and is employed by Etex Corporation.

Finally, in interest of the public transparency with respect to all other participants, we ask that they publicly disclose prior to making any remarks any current or previous financial involvement with a firm whose products they may wish to comment upon.

This statement will be available for review at the registration table during the meeting and will be included as part of the official meeting transcript.

Dr. Naidu.

DR. NAIDU: Good morning. My name is Sanjiv Naidu and I'm the Acting Chairperson of the Orthopedic and Rehab Devices Panel. I am Professor of Orthopedics at the Penn State College of Medicine. I'm an orthopaedic surgeon and also a material scientist.

At this meeting the panel will be responding to FDA's questions on the design of clinical studies for spinal devices to treat mild to

moderate low back pain. Before we begin, I would like to ask our distinguished panel members who are generously giving their time to help FDA in the matter being discussed today, and also the other FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation

Why don't we start off with Mr. Melkerson.

MR. MELKERSON: I am Mark Melkerson. I am the Acting Director of the Division of General Restorative and Neurological Devices and I'm a biomedical engineer.

DR. YASZEMSKI: I'm Mike Yaszemski and I'm professor of Orthopedics and Biomedical Engineering at Mayo Clinic in Rochester, Minnesota. I'm past chair of this panel.

DR. RUDICEL: I'm Sally Rudicel. I'm Associate Professor at Tufts University and I work at Tufts New England Medical Center in Boston.

DR. KIM: I'm Choll Kim. I'm an Assistant Professor of Orthopedic Surgery at the University of California, San Diego. I'm the Director of the Spine

Research Lab and Spine Fellowship Program at UCSD Medical Center.

DR. DIAZ: I am Fernando Diaz, Professor of Neurosurgery at Wayne State University.

MS. WHITTINGTON: I'm Connie Whittington. I'm an Orthopedic Clinical Nurse Specialist at Piedmont Hospital in Atlanta where I serve as the Coordinator for Research.

DR. NAIDU: Thank you, panel members. We will now proceed with the open public hearing portion of the meeting. Prior to the meeting eight organizations and manufacturers asked to speak at the open public hearing. They will speak in order of the request to speak. Each organization and manufacturer has 10 minutes to address the panel. We do have a speaker timer.

We ask you to speak clearly into the microphone as the transcriptionist is dependent on this means of providing an accurate record of this meeting. Please state your name and the nature of any financial interest you may have in this or any other medical device company.

Ms. Scudiero will now read the open public hearing statement.

MS. SCUDIERO: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of any individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your statement to advise the committee of any financial relationship you may have with the sponsors, which is not relevant for today exactly, its product, and, if known, it direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If

you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Sally, did you provide your statement?

DR. RUDICEL: Yes, I did.

MS. SCUDIERO: Thank you.

DR. NAIDU: The first open public hearing presenters are representing the Orthopedic Surgical Manufacturers Association, OSMA. Ms. Sally Maher, Esq., the President of OSMA, will speak first and Dr. Mathews will follow her.

Ms. Maher, I suppose you know the timer pretty well?

MS. MAHER: Yes. Ms. Feinway said I could have two minutes of theirs.

DR. NAIDU: Okay. So the two-minute warning will not apply to you.

MS. MAHER: Thank you. Good morning. My name is Sally Maher and I'm the President of the Orthopedic Surgical Manufacturers Association. OSMA is a trade association comprised of greater than 30 medical device companies who produce more than 85

percent of all orthopaedic implants intended for clinical use in the United States today.

We greatly appreciate the opportunity to address this distinguished panel.

In the interest of time I will focus my comments on three regulatory points, the least burdensome provisions of the FDA Modernization Act, regulatory thresholds for PMA approval, and a definition of valid scientific evidence.

Dr. Hal Mathews from the Medical College of Virginia will provide further comments from a medical perspective.

In 1997 Congress signed into law the FDA Modernization Act of '97. Congress stated that the central purpose of the act was to ensure the timely availability of safe and effective new products that will benefit the public and to ensure that our nation continues to lead the world in new product innovation and development.

The law states that FDA shall consider in consultation with the applicant the least burdensome appropriate means of evaluating device effectiveness.

It would have a reasonable likelihood of resulting in approval.

FDA has defined least burdensome to mean a successful means of addressing a premarket issue that involves the most appropriate investment of time, effort, and resources on the part of the industry and the FDA. We believe that is critical to keep in mind today the intent of Congress in passing this law, as well as the language in law and FDA's implementing regulations.

In that regard we wanted to share with you three important provisions that are contained in the least burdensome guidelines. FDA's guidance document states that if clinical data are needed, FDA and industry should consider alternatives to randomized controlled clinical trials when potential bias associated with the alternative controls can be addressed. Among the alternatives listed are study designs, employing nonconcurrent controls such as historical controls, objective performance criteria, and patients as their own control.

The least burdensome guidance document

also discusses the use of modern statistical methods such as phasing analysis to achieve a least burdensome path to market. Also, the use of scientifically valid surrogate endpoints and the use of Baysian analyses can predict longer-term data based on shorter-term follow-up thereby allowing a PMA application to be filed early.

Another important consideration is the role of post-marketing information to assure long-term device safety and effectiveness thus reducing premarket burden. When considering a clinical study design for the devices that are the subject of today's discussion, we would like to remind the panel of the regulatory threshold that has been established for PMA approval, a reasonable assurance of safety and effectiveness.

FDA's explanation of reasonable assurance of safety and effectiveness is based on providing valid scientific evidence. It is noteworthy for this panel that several alternatives to randomized control clinical trials are included in FDA's definition of what constitutes valid scientific evidence.

Finally, I would like to provide some brief comments regarding the specific questions that are before you today. With regard to Question 1, it is OSMA's opinion that the decision regarding the time to surgically intervene should be dictated by the standard of care for the specific indication.

We note there are guidelines published by the American Academy of Orthopedic Surgeons in this regard, as well as recent publication in the Journal of Neurosurgery which outlines treatment guidelines for degenerative disc disease.

Furthermore, in answering this question, one must consider the standard of care, the intended use of the device, the patient population for which the sponsor seeks approval for the device to treat, the risk of the investigational device, and the health benefits that the sponsor seeks to prove.

With regard to Question 2, OSMA believes that the panel cannot categorically assign a control treatment group to each device category. First, the demonstration of effectiveness might involve alternatives to randomized controlled clinical trials

such as historical controls using patients as their own control, or use of a concurrent nonrandomized group control.

Second, this decision should be based on the intended patient population and the health benefits that the sponsor is seeking approval to promote. As with the selection of the comparison treatment or control group, the determination of the clinical trial entry requirements should be based on the study objectives.

With regard to Question 3, OSMA believes that endpoints cannot be categorically assigned to each device type. Rather, a sponsorship propose a set of endpoints that they believe will yield valid scientific data to support the study hypothesis and the intended use of the device.

Particularly for early intervention motion preserving devices, study sponsors should be able to use a shorter-term data to demonstrate safety and effectiveness rather than placing all the emphasis on long-term follow-up which historically derives from the time to develop a fusion mass.

Patients want relief from their pain and they want to go back to work. Therefore, we believe that shorter-term endpoints should be considered valid in supporting PMA approval for the subject devices.

With regard to Question 4, OSMA supports the option to allow both smaller changes in pain and function scores and flexibility in the traditional delta between comparisons or treatment groups based on the study objectives and the proposed claims to the device.

In conclusion, the OSMA member companies would like to leave you the following two points. We believe that the questions and issues presented to the panel today are too complex and multi-dimensional to make any conclusive determinations in just one morning session.

The clinical trials' issues outlined in FDA's questions should not be discussed without serious consideration for the least burdensome provisions of the FDA Modernization Act, the threshold for PMA approval, and the definition of valid scientific evidence.

We greatly appreciate the opportunity to address this distinguished panel today and hope our remarks will be taken into your consideration as you discuss this. I have given you a much thicker speech that you should read and enjoy before the end of the day. Dr. Mathews will discuss the clinical perspectives. Thank you.

DR. MATHEWS: Thank you. Good morning. My name is Dr. Hal Mathews, and I am a spinal surgeon from Richmond, Virginia. Although OSMA has paid a portion of my travel expenses today, my comments reflect my personal views, and they are not necessarily consistent with the views of each of the orthopedic companies comprising OSMA.

I would like to focus my comments today on a clinician's perspective of the four specific questions that FDA has posed to this panel and the three different types of implants being considered today.

First, FDA is seeking input on the clinical study of early surgical interventions in lumbar degenerative disc disease. Three different

types of implants are to be considered are interspinous process spacers, nucleus replacements, and pedicle screw/dynamic stabilization systems.

Through the years, I have consulted with companies on product designs and clinical study designs. In the past, we have tried to force-fit studies into a certain design to decrease the amount of time needed to gain regulatory approval.

As a collaborative, forward-looking exercise, I believe the guidance provided by the Agency should not map designs to device types, but should be flexible enough to assist in resolving study design questions for the early intervention under discussion today as well as for those that may not yet be conceived of or designed.

With respect to the first question about the appropriate time needed before intervention with an implantable device, it is my opinion that symptomatic lumbar degenerative disc disease can be viewed as a continuum, depending on the severity or progression of the disease.

In my practice, conservative care options

for patients early in this continuum would include rest, change in activity status, exercises, physiotherapy, NSAIDs, and possibly steroid injections. I believe that these patients could become surgical candidates if their symptoms did not subside over several weeks of treatment or if an identified pathology, such as an annular tear with or without herniation, progresses.

These patients may be candidates for nucleus replacement if their symptoms do not relent after a several weeks. These patients could also receive a pedicle screw system if their symptoms are longer-standing or if the annulus needs retensioning.

The FDA's second question pertains to the appropriate control groups for studies involving the three subject devices. I have to point out that a device could treat multiple indications, and I believe that appropriate controls have to be based on indications and treatment goals, not necessarily on the devices themselves.

Also, we should not automatically jump to the requirement for a randomized, controlled clinical

trial. It is legitimate to design studies with patients as their own controls or with historical controls. Conservative care controls may also be appropriate if handled adequately in the protocol, such as, for example, existing care data from other physicians or a treatment cross-over.

Regardless of the control chosen, care must be taken to make sure that it represents an appropriate comparison treatment. For example, it would be inappropriate to utilize a more invasive control that is a standard of care for a later stage of degenerative disc disease if the investigational treatment is intended for an earlier stage of degeneration. I would recommend guidelines similar to those of AAOS guidelines as references in designing protocol criteria.

The FDA's third question to this panel focuses on the selection of appropriate study endpoints, when to evaluate these endpoints, and the importance of certain radiographic measures. First, I need to emphasize that these are not spinal fusion devices; rather they provide spinal stability, thereby

reducing or eliminating the patients' symptoms.

Historically, FDA has desired 12- to 24-month data as a prerequisite for device approval. One possible reason for this is that they believe that it takes this long for the spine to fuse. However, short-term data may be sufficient for approvals of these devices when stability, and not fusion, is the objective.

I believe that 12-month data, perhaps even less, would be adequate to determine the safety and effectiveness of early intervention non-fusion devices. If the FDA desired longer term data for added comfort with their approval decision, post-approval patient follow-up studies could be employed.

I also believe that device effectiveness should be based more on alleviating patient pain and restoring function rather than on radiographic measures. Spinal stability without pain relief is not an effective device treatment. Conversely, both patient and surgeon may be satisfied even if the radiographic criteria are not met but the patient is pain-free and has resumed the desired lifestyle.

Therefore, I recommend that tools such as Oswestry, Visual Analog Scale, and SF-36 scales be used alone or together to evaluate patient outcome. Perhaps, there are other, more newly validated, and perhaps more sensitive, tools that would detect early post-operative treatment benefits. Patient satisfaction, perceived treatment effect measures, and work or activity status may also be incorporated.

When analyzing and interpreting the data, emphasis should be placed on early postoperative time points since these types of devices are intended to provide benefits to the patients early on.

Finally, I would not recommend that radiographic criteria serve as a primary endpoint. For these devices, radiographic data is "nice-to-know" information that should be collected and presented. However, the approvability of the device should not hinge on it.

FDA's last question relates to the threshold for determining device effectiveness. Since the types of spinal implants being discussed here today are generally intended for earlier states of

lumbar degenerative disease and, in some cases, require less surgical trauma and rehabilitation, the success criteria and statistical approach should take into consideration these differences.

In conclusion, I hope this panel and the FDA have found my comments useful. I believe the safety and effectiveness of these devices can be determined via a number of approaches, all of which appear to be less burdensome than current IDE study designs. I advocate smaller studies based on shorter-term endpoints. Device approvals can be accompanied with requirements for longer-term post-market patient observations.

My final comment to you is to encourage innovation and flexibility in study designs. With the types of devices being discussed here today and for those of the future, there cannot be a "one size fits all" randomized controlled study solution. Study measurements will have to be molded around the product indications, the intended patient population, and the study objectives. I encourage everyone to be open to novel ideas.

I appreciate your attention. I will be here most of the day and would be glad to try to answer any questions you may have. Thank you.

DR. NAIDU: Thank you, Dr. Hallett.

Next we have representatives from Spine Wave. First is Mr. Ronald Smith, Director of Quality Systems and Regulatory Affairs and then Mr. Pafford will follow.

MR. SMITH: Actually, just a point of clarification. Mr. Pafford will not be speaking. I will be speaking to all the points.

DR. NAIDU: Thank you.

MR. SMITH: Good morning. Good morning. My name is Ronnie Smith and I am Director of Quality Systems and Regulatory Affairs at Spine Wave, Inc. Spine Wave is a small medical device company located in Shelton, Connecticut.

Having spent the past few years developing a nuclear replacement device, Spine Wave appreciates the opportunity today to present our thoughts on issues surrounding the time course of treatment for patients that would be possible candidates for nucleus

replacement or augmentation surgery.

During the next few minutes, I would like to briefly introduce our nucleus replacement technology so that you may have a better understanding of how this device when used in two distinct indications, each with different conservative care regimes fits into the continuum of care for the spine patient.

Specifically, I will speak to its use as a nucleus "augmentation" device for patients facing surgery for herniated nucleus pulposus as well as a nucleus "replacement" device for patients with chronic degenerative disc disease.

In closing I will also discuss the company's position regarding the appropriate time for surgical intervention for these types of devices for each of these distinct uses.

Spine Wave's NuCore Injectable Nucleus is an in situ curing material that is designed to have properties that mimic those of the natural nucleus pulposus. The material adheres to the existing nucleus pulposus and to the annulus and, once cured, mimics

the human disc nucleus in protein content, water content, pH and mechanical properties.

Unlike most other types of nucleus replacement devices that we are aware of, the NuCore device replaces only what has been removed. Therefore, the size of the implanted device is determined by the amount of nuclear material the surgeon removes.

The shape of the implanted device is determined by shape of the space into which the NuCore material is injected. This is distinct from many other nucleus replacement devices, which are typically preformed devices either produced from preformed hydrogel or other Spine Wave panel Comments.
This also differentiates the NuCore from other products that are injected into a containment system which determines the amount and size of the replacement.

The physical, chemical and mechanical properties of the NuCore Injectable Nucleus allow for multiple potential intended uses within what is referred to generically as lumbar "degenerative

disease." For example, one indication for Spine Wave's technology includes replacement or augmentation of nucleus pulposus material through injection into the void created after a standard discectomy for a herniated nucleus pulposus.

Disc nucleus herniations are generally "acute" events; unlike the "classic," chronic degenerative disc disease paradigm. These acute herniation patients may present with unremitting low back pain in addition to sciatica. When nucleus material is herniated from a disc, or if a surgeon removes nucleus material from the disc, the mechanics of that disc and at the operated level change and the conditions are established for subsequent degeneration.

Even though patients undergoing removal of the nucleus material without replacement in a conventional discectomy procedure may often yield a good "short term result" based on pain scores, studies have shown that many of these patients go on from the acute herniation to subsequent degeneration as well as re-herniation and re-operation.

As with other nuclear replacement devices being developed, the NuCore Injectable Nucleus also has potential benefit in the treatment of those patients who have "chronic" degenerative disc disease. These devices are intended for patients with mild to moderate low back pain with classic signs of degenerative disc disease, as opposed to the acute herniation injury described previously.

These patients, if left untreated, may progress through more severe stages of degeneration, which may ultimately require fusion or disc arthroplasty.

With either of these two distinct intended uses for the NuCore Injectable Nucleus, this device would be considered by FDA to be a "Nucleus Replacement Device." However, while both sets of patient populations would be diagnosed generally as having degenerative disc disease according to FDA definitions, the treatment modalities for each population would be distinctly different.

As such, if each intended use were to be studied clinically, they would likely each use a

different control group for comparison. Therefore, in giving its recommendations to the Agency, we would urge the panel to be aware that nucleus replacement devices may be intended for different clinical indications.

The type and duration of conservative care that a patient should receive prior to use of such a device should be dictated by the clinical condition being treated, not a technology classification. The surgical treatment guidelines for acute disc herniations are very different from those for chronic degenerative disc disease, particularly with respect to conservative therapy timing.

A patient with a herniated disc has generally suffered an acute "event" as opposed to a chronic or progressive "disease" and the consequences of this event can progress rapidly and with great severity. It is for this reason that we feel that the most appropriate course of action for the treating physician is to follow guidelines, such as those established by the American Academy of Orthopedic Surgeons, Washington State, or by the Agency for

Healthcare Research and Quality that apply to the condition being treated.

All of these guidelines establish a course of treatment only after establishing a differential diagnosis. According to the AAOS guidelines, these differential diagnoses are:

1. Herniated Nucleus Pulposus (HNP)
2. Unremitting Low Back Pain (LBP)
3. Spondylolysis or Lytic Spondylolisthesis or Degenerative Spondylolisthesis/Stenosis (SLIP)
4. Spinal Stenosis

As outlined by the AAOS guideline, a full course of nonoperative treatment for each diagnosis should first be considered for mild to moderate conditions unless it is clear that the patient falls into the clinically severe category. In the case of a diagnosis of herniated nucleus pulposus, initial nonoperative treatment for mild to moderate conditions is recommended for four to six weeks.

If unresolved, the HNP patient should be referred to a specialist for further discussion of treatment options, including operative treatments such

as discectomy. However, if the patient presents with a profound/progressive neurological deficit, disabling leg pain or loss of bowel and bladder control, therefore falling into the "clinically severe category," the patient moves directly into a management decision between the patient and physician regarding continued nonoperative treatment versus operative treatment.

These patients may or may not have completed the outlined conservative treatment course but it would be a disservice to these patients to be denied the possible benefit from new technologies simply because they didn't meet a "time" requirement established by an Agency guideline.

In contrast, the agency has typically required the conservative treatment period to be six months for studies which are intended to treat any degree of degenerative disc disease in the lumbar region. The agency's recommendation clearly does NOT correlate with AAOS guidelines for management and treatment of patients with acute herniated nucleus pulposus.

It is for this reason that we would recommend the agency adopt a guideline such as the AAOS guideline which was established by physicians that are expert in the field of spine surgery to not only define patients who are appropriate candidates for surgical intervention, but to establish an appropriate course of treatment and time frame for this treatment.

Criteria for inclusion of patients in the clinical study of a new device should be determined through such guidelines by the surgeon, and should be tailored the specific indication and patient population under study.

In conclusion, we appreciate the panel considering these points and would like to again thank FDA for the opportunity to make these comments. Thank you.

DR. NAIDU: Thank you, Mr. Smith. Representing Zimmer Spine we have Dr. Reginald Davis of the Greater Baltimore Medical Center. Dr. Davis.

DR. DAVIS: Good morning. My name is Reginald Davis. I'm a neurosurgeon in clinical

practice. For today's discussion I am a Zimmer paid consultant being reimbursed for my time away from my practice. I am involved in several clinical trials. I currently am one of the principal investigators for the Dynesys IDE study currently ongoing in the USA.

The comments I will make are my own composition. The words and thoughts belong to me and me alone. I appreciate this opportunity to represent my own thought processes to this panel.

Lumbar degenerative disease actually represents a broad spectrum of a complex cascade of processes. They are unique characteristics specific for each individual portion of the anatomy of the spine that has to be considered independently if a proper algorithm is going to be proposed.

The disc has a specific pattern of degeneration. Initially with the mild disease there is maintenance of disc height, relative maintenance of hydration so there is minimal radiographic findings even though there may be significant pain.

As the cascade progresses with moderate disc disease we see loss of this disc height, loss of

this hydration. Some annular fissures may occur. There may be some end plate changes or early modic changes.

As the progression continues you get into the severe cases which is characterized by disc space collapse, vacuum phenomenon. Similar stratification, a similar process occurs with the other structures of the spine, the sets, the ligaments leading to stenosis and lateral recess encroachment, even the vertebral body with development of sclerosis, osteocytosis.

All of these have to be characterized and there is a summation of the characterization of each of the anatomical structures that can lead then to a characterization of the overall lumbar disc disease such that severe disease across the board will result in a diagnosis of severe lumbar disc disease.

With this stratification I think a logical algorithm or logical nature is going to be developed to promote guidelines for how these devices can be looked at. The patients likewise can be stratified. The patients themself have a physical component. They can be healthy to chronically ill with multiple co-

morbidities.

Patients themselves can be robust to fragile, young to elderly. They cover a broad spectrum and these are independent of the disease process. The disease process itself can be acute occurring within days to weeks. It can be chronic or end stage having progressed or grown out of the course of many, many years.

Psychologically patients also stratify themselves ranging in characteristics from well adjusted, self assured to psychologically impaired, co-dependent, and very dysfunctional. The socioeconomic support structure of the patient also comes into play with the psychology. They can have good family support, good church support, good economic backup all the way to complete collapse and total failure of the socioeconomic support.

This allows stratification of the patients into good or excellent physical specimens, average or poor. Psychologically the patient is stratified into well adjusted, moderately maladjusted or severely maladjusted. These variables are actually independent

of the lumbar disc disease process itself. This allows a selection bias for the best study outcome.

Only the better patients will get enrolled in study even though this may not truly represent our own personal clinical experience.

Subsequently, there is a possible discrepancy that develops between these study results and the subsequent clinical results. I think that any ongoing consideration to guidelines must take this into consideration as well.

The treatment options likewise form a spectrum. That allows stratification with proper analysis. The nonoperative treatments, medications, rest, physical therapy, pain procedures including injections and some minor ablation procedures such as rhizotomies and IDEs.

Decompression would be the next major category with tubular decompression being the least invasive all the way through to major laminectomy and facetectomy which may introduce an element of instability.

Then fusion. Even the fusion can be

substratified into minimally invasive. Posterior or anterior fusion. And then posterior and anterior fusion, so-called 360, are representing the most severe surgical invasiveness or treatment option in this category.

Such the stratification comes in to nonoperative and minimal surgery, which tend to be out-patient, not invasive, minimal blood lost basically characterized by no disruption of the native anatomy. Certainly disruption of the fascial planes but nothing else.

Moderate surgical interventions then would be moderate disruption of native anatomy or removal of some of the bony structures. This tends to be an in-patient procedure with moderate blood loss. Major surgical intervention would then be a significant disruption of the anatomy with significant removal of some anatomical structures and significant alteration of the physiology.

With these stratifications in mind, the devices themselves allow for stratification. Based on invasiveness they can be minimally invasive to totally

invasive. Based on reversibility the device itself can be removed with the native anatomy being left relatively intact resuming native physiology.

They can be revised or not be revised. They can be removed with placement of a new device or a similar device or totally revised to a different category, or they are permanent requiring a totally different approach for revision.

Then there is the familiarity of technique. It ranges in spectrum from very well known familiar technique to all surgeons to requiring novel approach or techniques. Subsequently the devices stratification have the following characteristics showing minimal fascial disruption, the reversible, revisable with familiar techniques.

Moderate acuity devices do require bone disruption. Removable, revisable still but perhaps with some residual physiology alteration. And then variation on a known technique. The major devices or interventions will require removal of major anatomical structure with subsequent significant alteration of the physiology. They are not reversible or easily

removable and require a novel approach or brand new technique, a substantial learning curve for the surgeon.

I think the evaluations themselves if they are well known and well accepted can also be stratified on the basis of minimal, moderate, and major, VAS, ODI, SF-36. Certainly the data that's obtained is worthwhile. However, how it's applied can be stratified and individualized for each device in each patient group as study outcome.

Radiographic study needs to be tailored specifically for that portion of the anatomy that's being structured and is used for screening or used for staging of the disease process itself but in and of itself should not be used as an endpoint for device acceptance. Then standard criteria appropriately applied, I think, will be the key to flexibility.

We need to be able to apply these in equivalence studies versus superiority studies depending on the study design. Then being able to analyze the trend of net change versus the overall average value which will vary from patient acuity to

patient acuity.

Utilizing all of these characteristics and proper analyses I think that a rational matrix can be obtained. If we look at the spectrum and stratification and apply these across the board, then the guidelines kind of define themselves based on the individual device.

For example, as my experience is with the dynesys, stratification of this pedicle screw base device for treatment of these syndromes, it is revisable and it is reversible. It has a familiar technique. It does require bone disruption. Therefore, this represents a moderate intervention and should be applied in moderate instances and moderate patients.

The moderate disease characteristics would be radiographic evidence of moderate degenerative disease with some tubal body collapse, neural impingement with subsequent symptomatology. The ligament has laxity which may lead to a spinal lithosis and moderate facet changes as evidenced by CT.

The patient would also have a sub-acute to chronic onset having failed physical therapy of at least six weeks but more in the course of three months so this would not be immediate intervention but more the moderate onset intervention.

The treatment options and, therefore, the control group or the control surgical group should also be of a moderate category so this can be compared to a major decompression which is perhaps a little less than the dynesys and, as such, the dynesys would have to demonstrate superiority given this matrix.

Or it can be compared to a moderate intervention of posterior fusion in which case they are fairly equivalent and, as such, utilizing the analog scales and the various in modalities for assessment equivalence, would have to be demonstrated. I feel that especially in the face of fusion that this would have a time frame of one to two years.

However, for some of the minimal devices that time frame should be modified accordingly. With acute intervention, acute treatment options, and comparison to acute processes, I think the time frame

and the analyses should also be acute.

I thank you for your attention and hope that you will take into consideration that in order to move forward with proper guidance, guidelines for these devices flexibility and analysis of each individual criteria would have to be the rule of thumb. Thank you.

DR. NAIDU: Thank you, Dr. Davis.

Next representing Abbott Spine, Emerging Technologies Research and Development will be Dr. Paul McAfee of Towson Orthopedic Association, and Brent Blumenstein of TriArc Consulting.

Dr. McAfee.

DR. McAFEE: Thanks very much. I'm a consultant for Abbott Spine. I do not have a financial interest in the products. I drove from Baltimore.

I'm going to show some slides that highlight some of the points. We've had very productive dialogue over the past year with the FDA so my comments will be more specific than many of the other talks.

In short, we've had an approved IDE to start and the control group was total disc replacement and PLIF with pedicle screws. But our investigators at our 20 investigator sites felt that the control group was a larger magnitude of procedure than the Wallis. Essentially myself and Dr. Blumenstein are going to present what we feel to be a good experimental design for the control.

The inventors is J. Sènègas. It's a nonrigid fixation system. It does not use pedicle screws and is intended for degenerative changes less than Pfirrmann State V. Both N. Simon and Brian Cunningham have shown that the Wallis reduces the extremes of flex and extension by 35 percent.

The advantages of the Wallis, it's largely a soft tissue procedure can be performed as outpatient, no general anesthesia required. There's no spinal column structural removal, only the interspinous ligaments. The rehabilitation is much faster. It's on the one to two-week scale versus three to six months recovery for spinal fusion. The device can be removed without requiring a fusion or

anterior rate vessel dissection.

It is a very safe procedure. This is a 16-year survivorship experience from Sènègas. They obtain follow-up on 58 percent of the patients and the survivorship at 16 years was 82.7 percent. Only five devices were actually required to be removed. This is very competitive and compares very well with what I have had the opportunity to present to the panel a year ago. This is the reoperations on the Charité, 4.9 percent versus the BAK fusion control of 8.1 percent.

Now, there is also an international study on the Wallis in six different countries, 262 patients with a minimum of one-year follow-up. It is intended for degenerative changes less severe than either the Charité or a PLIF. It's Modic Stage 1 or less. There has to be less than 50 percent loss of disc space height.

The VAS going from a mean of about 70 down to 15 is very competitive with the functional outcomes at one year for either fusion or disc replacement. One definite advantage with some of the data the

company has collected, there's 55 matched sets of MRI, pre-op and at one year. It does show in a majority of cases rehydration of the nucleus pulposus. There is the opportunity for regeneration or repair of the disc by protecting the extreme range of motion.

For example, on this picture of this 36-year-old woman you would match up the hydration signals at L3-L4, and L5 S1. You match up the hydration signal of the uninvolved level. I think you can see some definite changes and rehydration at L4-L5.

So our preferred experimental design is not the Wallis versus conservative physical therapy, but it's the Wallis versus conservative treatment plus a rescue procedure. The rescue procedure can be invoked as early as eight weeks. The rescue procedure is a fusion or arthroplasty. It's not a cross-over to a Wallis. The rescue is permanent and with no clear revision strategy. It has the potential for the neurologic morbidity and vascular problems.

One of the key concepts we want to get across is that if you look at the randomized study,

205 Charité patients versus 99 of EAKs. There is a durability of response that occurs at six months so at six months both the VAS and the Oswestry were very predictive of the 24-month results.

We feel once a patient crosses over -- I'm sorry, once a patient is rescued, then you need to get a good response and if that response is maintained for six months, then that is worth something clinically. The advantages are, aside from the reversibility of the Wallis, the fact that it's just largely under the fascial posteriorly, does not involve any dissection of the neural elements as a PLIF would.

It can be placed through a two-inch incision on out-patient. It leaves the option for fusion and total disc replacement completely open. I hate to use the cliche' but it does not burn any bridges.

On the left is Pfirrmann's classification which is not widely used but at Pfirrmann Stage 1 in the upper left, that's fine to use physical therapy and epidural injections. In the lower left is a collapsed disc. That's fine to do a PLIF and a disc

replacement but we attempt to treat patients with Pfirrmann II, III, and IV so we are addressing the strategy to those patients with the intermediate amount of degeneration.

On the right is Pollintine's work. It's very important to show that you go all the way up to a degenerative Stage IV before you get irreversible changes in the facet joints so you have three stages of degenerative changes involving the anterior column. Our device, and other interspinous devices are aimed at trying to intervene earlier and preserve those posterior facet joints.

Thanks very much. In summary, just with my theme of being specific, I would try to go for a delta of 15 percent versus 10 percent. I feel this is justified because the procedure can be done on an out-patient, local anesthesia, faster rehab, and it's more reversible.

Secondly, as a clinician I'm willing to accept a five percent lower success rate for the Wallis versus the more invasive total disc replacement or PLIF due to the fact that it's reversible and it's

largely superficial just under the lumbar facet anywhere from L1 to L4. Thanks very much.

DR. NAIDU: Thank you, Dr. McAfee

DR. BLUMENSTEIN: I'm Brent Blumenstein, statistical consultant to Abbott and they do pay me.

What I wanted to do today was to propose a design for this class of devices. The purpose of this chart is to show the three relevant types of devices that we are talking about here, the current focus on what I've labeled for this presentation as early invasive intervention.

The point here is that there is a radiant of invasiveness, risk, and whether or not subsequent interventions are possible. This has an influence on what type of outcome one focuses on. For conservative care you're looking for durable success of some kind which is a good thing. With this new class of devices we are also looking for durable success which is also a good thing.

Whereas in the traditional late invasive interventions the focus is usually on failure to realize success or a failure to sustain success.

These are really bad things as opposed to good things. So what we propose as an outcome of interest to be in a trial is what we call a durable response. This is the realization of the state of response for all assessments spanning at least X months.

The criteria for state of response has specific elements discussed by others. It's for changes and things like that. You can put whatever you wish in here. We are proposing that this X be six months. That is, if someone has a response that it be observed for at least six months to be called a response.

We feel this is clinically meaningful relative to the characteristics of the type of device that we're talking about here. If you have a group of patients treated with one of those devices, a high proportion of this durable response implies efficacy. So that's all well and good but when we get to the statistical considerations we want to take it one step further.

What we have here is the proposed statistical input of time to durable response. The

reason we do this is because the speed at which these responses occur is actually quite relevant to the type of device that we're talking about today. What we mean here is the time interval from randomization until the date where the durable response is observed to start.

It is important to realize that when you convert a dichotomous endpoint of a durable response to a time to that endpoint that you have to take certain things into consideration. One of them is that this is subject to competing risk. Competing risk is something that prevents observation of the endpoint and that would be death or revision or whatever.

That is, these things prevent you from observing a durable response. A competing risk is not the same thing as sensoring due to lack of follow-up. What we want to do with this proposed endpoint is to look at the cumulative incidence of these in our statistical considerations now that the vertical axis has dropped here.

This is proportion, this is time, and this

is the proportion of patients in each of these two arms that have experienced the durable response to the specific point in time dating from the date of randomization. At one year you have this percent of patients in the control arm and this percent of patients in the investigational arm having achieved a durable response.

So when we think about control arms for trials of early invasive intervention, we find out that we don't have a predicate at this time and, therefore, we really can't think about a superiority or non-inferiority trial against the predicate. What we are left with is conservative care or late intervention.

If we think about using late invasive intervention as our control arm, we have to think about that it's okay if the late invasive intervention is superior to the early invasive intervention because the early has lower risk and it also doesn't preclude subsequent intervention.

The issue here is defining an acceptable degree of inferiority. That would be the separation

at a prespecified time. For example, 24 months in this cumulative incidence that we're talking about. We would call this an acceptable inferiority trial as compared to a non-inferiority trial.

Here is the representation of what it might look like. This is the investigational arm. It has a very rapid increase to a plateau of success. Whereas, the control arm has a slower increase followed by a possibly higher ultimate outcome.

This is inferior at this point in time, for example, and so the acceptable inferiority has to do with this margin that you are willing to accept given the less invasiveness and potential for revision.

Now, if we think about taking instead the control as just conservative care as opposed to the late invasive intervention, we can think about that as the time to durable response outcome is appropriate. We can think of this as being a superiority trial.

What we immediately come up against is what if the early intervention is almost surely superior to conservative care? In other words, almost

a given thing. Also, this trial wouldn't address long-term effects. In other words, the reversing of the early invasive intervention.

So what we are proposing instead is a conservative care with rescue. What this does is it allows the control arm to catch up to the early invasive intervention when we are almost surely superior to just conservative care. What we have here is a rescue implemented in the control arm only.

This rescue should not be the early invasive intervention. In other words, the so-called "crossover" would not be applicable to this. The rescue would be something more, a late invasive intervention.

What we are going to propose is two endpoints and the primary endpoint we are calling it a short-term endpoint and it's just time to durable response from the first intervention. In the early invasive intervention is what we mean by the first intervention in the investigational arm.

Conservative care is the intervention of interest for this endpoint in the control arm. This

would be just to compare the cumulative incidence curves for that primary endpoint. This would be what it would look like. We would have a more rapid and a higher investigational arm cumulative incidence of durable response, whereas the control arm would be lower. We would probably win on that one.

But the co-primary endpoint that captures the long-term outcome would be a durable response cumulative incidence at time Y where we are going to define Y as 1. What we're talking about here is that the conservative care durable response includes the rescue intervention and ignores conservative care failure. What we are doing is deferring what we consider to be the intervention that might cause a durable response.

It could be either conservative care or the rescue procedure. What we would do here would be compare the durable response cumulative index at time Y. We are proposing Y as 1 year because the early invasive intervention likely has a rapid onset of benefit and fewer complications.

Some more considerations. The requirement

for superiority of the investigational arms and for this co-primary endpoint seems onerous. In other words, I'm not sure that you could really expect an early invasive intervention to be superior in the long run to the late. We've already discussed this point before.

So we could test for either noninferiority or this acceptable inferiority trial. This is the situation where the outcome would be equivalent. That is, we have a rapid onset but a flattening versus the came long-term outcome but less speed in getting there. This is the situation where the investigational arm has a rapid plateau but the control arm is slower to get there but it gets there higher. This is maybe the acceptable inferiority margin.

So there are other issues to solve. Many of these will be discussed today, eligibility, criterion for implementing the rescue intervention, which rescue interventions are used, and should the investigational arm also be allowed to be a rescue. We think not. Then there's this secondary endpoint

that you would measure would be there as supportive such as time to failure of the device.

In summary, what we are recommending is the control arm be conservative care with rescue, that the primary endpoint for short-term should be a time to durable response from the first intervention analyzed using cumulative incidence methodology, and that the co-primary endpoint would be a long-term endpoint. It would be a cumulative incidence difference at 1 year between the two arms. This could be either set up as noninferiority or as acceptable inferiority.

I'll be around today.

DR. NAIDU: Thank you, Dr. Blumenstein.

Next representing Stryker Spine we'll have Dr. Eeric Truumees of Weisman, Gitlin, and Herkowitz of William Beaumont Hospital.

Dr. Truumees.

DR. TRUUMEES: Good morning. My name is Eeric Truumees. I'm a local spine surgeon in private practice with Weisman, Gitlin, and Herkowitz. I also maintain an active academic practice and run a

biomechanics laboratory at William Beaumont Hospital in Royal Oak, Michigan.

I'm a paid consultant with Stryker Spine and they funded my travel and lodging costs in order to attend this meeting. I greatly appreciate the opportunity to address this distinguished panel today and comment on the questions posed by the panel.

First, I would like to acknowledge the FDA's concerns. The human study of these new, early intervention devices creates novel challenges for clinical trial design. Prudent and ethical study of medical devices in degenerative conditions requires appropriate attempts at non-operative management.

Further, appropriate operative intervention is offered once our patient's symptomatic progression has become clear. That is, early surgery may be unnecessary surgery in the sense that some patients' symptoms could improve without surgery.

Finally, to understand the real effects of implantation of a given device on that patient's clinical status requires careful study with appropriate comparison groups and sensitive outcomes

measures.

While I agree with concerns that generated the questions we are here to address, I feel that these questions make false assumptions about this category of devices. Global answers are being sought for groups of implants that have very little in common.

FDA seeks to prescribe relatively uniform approaches to the study of these new devices. In so doing, the marked differences in the goals, intended patient population, mechanism of action, and the level of surgical morbidity are ignored.

Overall, clinical goals and expected outcomes are much different. Rather than establish a list of acceptable controls for the study of a particular implant group, I would argue that controls, non-operative treatment periods, and outcomes measures should reflect the patient population, disease state under study, and device claims.

With regards to Question 1, the standard of care is best set by physicians, investigators and study sponsors and not by a regulatory body. While

there are a host of reasons Regulatory Bodies should not prescribe care to patients individually or in groups, the most important lies in the heterogeneity of the patients studied.

More specifically, lumbar degenerative disease is not a linear progression of symptoms and radiographic findings.

Patients with similar symptoms will vary markedly in their radiographic appearance. Similarly, patients with similar radiographs may have markedly different symptom profiles. Lumbar degenerative disease is best characterizes as a matrix of symptoms, functional effects, and pathoanatomic findings.

In patients with painful disc degeneration and identical symptoms and MRI findings, for example, the rate at which their facets degenerate or they lose back muscle can be very different. An appropriate time line for operative intervention in someone that is clinically stable is very different from the patient that has marked functional decline.

As a physician, I make decisions for a particular patient at a particular time in the

progression of their condition. I look at how symptoms affect a patient's life and perform a risk/benefit analysis of the various types of treatment options available.

We can't presumed that withholding intervention with a patient will protect them from overly aggressive treatment. Nor can we assume that the disease manifestations or pathology will become clear over time. Delayed intervention in some cases may require a more invasive approach later. That is, unlike with fusion surgery, waiting too long may preclude effective utilization of these new and novel treatment modalities.

Although some non-surgical treatment is always appropriate, we need to understand that the percutaneous placement of some implants are really blurring the lines between traditional nonoperative care and operative management. In some cases conservative management may be physical therapy, injection therapy, or may even be relatively less invasive surgery types.

Furthermore, one can not dictate in

advance of the emergence of a new device whether a four-week or four-month per of nonoperative care appropriate and what types of nonoperative care are nonoperative care are appropriate for your patient group.

With regards to Question 2, an appropriate control group should be chosen by the investigators and the sponsor based on the patient population under study and health benefit the sponsor is seeking approval to promote. The natural histories of all of the various types of painful degenerative lumbar disease remain insufficiently documented.

As such, the establishment of formal lists that allow controls for the study of a given class of early intervention device would be misguided. Even within the subgroups of nuclear replacement, for example, are devices that are implanted percutaneously and others that require formal, open surgery. These differences in approach will lead to differences in the ideal control groups for the individual devices discussed.

With the opportunity to investigate the

effectiveness of early intervention devices, nonoperative care may not always be an appropriate control group. However, in cases where a nonoperative control is used, from a patient care point of view, these must be allowed to cross over when appropriate. I believe that "appropriate" must be decided by the investigator and would be very difficult to define in a general guidance.

With regard to Question #3, as an investigator in several IDEs, I believe that study endpoints cannot be categorically assigned to each device type. Because of the marked differences and the goals of these devices, the sponsor in collaboration with clinician investigators should be free to propose a set of endpoints that they believe will yield data to support their study hypotheses.

Interspinous process devices, for example, are not a homogenous group. They have very different goals. One seeks to treat patients with neurogenic symptoms in a stop-gap approach to delay more invasive intervention such as laminectomy. Others seek to limit painful motion in patients with mechanical pain.

This difference in surgical goals should lead to very different outcomes measures and evaluation time points.

Along the same lines, we may use more subtle outcomes measures and demand far longer follow-up for devices seeking to prevent post-operative adjacent segment change than we would for a similarly configured dynamic rod device implanted to alleviate the low back pain. For the majority of devices, pain relief and functional outcomes remain primary measurements for success. Radiographic results are secondary endpoints.

As to the length of follow-up, points less than 24 months are sometimes appropriate, again, depending on the intended use and proposed benefits of the device. Twenty-four month endpoints are appropriate for morbid, open spinal reconstruction procedures requiring fusion.

For many patients undergoing these procedures, ultimate symptom resolution and return of full function doesn't occur until much later after the surgery. Given the less invasive surgical strategies

for some of these novel implants, outcome measures might become clearer much sooner. Therefore, the endpoints should match the proposed benefit of the device.

With regard to Question #4, I support the option to allow study sponsors and statisticians to specify study design based on the population studied and the objectives of the device rather than refer to standardized approach based on the outward appearance of the implant.

The challenge for industry, clinician investigators, as well as FDA, is to design and execute studies in a least burdensome fashion. That occurs in a complex clinical and regulatory environment in which some requirements seem to be at odds with one another.

In the end, our common goals are to help patients improve their quality of life or prevent further deterioration, and to do so with treatments and/or devices for which there is a reasonable assurance of safety and effectiveness.

Again, rather than standardizing study

designs based on the implant design, investigators and sponsors welcome the opportunity to work with the Agency to define study designs appropriate for the patient group implanted and the specific goals of the device. That is, less risky surgeries with lower morbidity should really have smaller -- be appropriate to have smaller clinical benefits.

Thank you for your time today. I hope my remarks were of value. I'll be available for questions as the day goes on.

DR. NAIDU: Thank you, Dr. Truumees.

Next representing North American Spine Society is Dr. Philip Schneider.

Dr. Schneider.

DR. SCHNEIDER: Thank you. Hello. Good morning. As you can see, I am not Dr. Marjorie Eskay-Aurbach as you have on your agenda. My name is Dr. Phil Schneider, and I am replacing Dr. Aurbach.

I am an orthopaedic spine surgeon in private practice, about 15 minutes from here. I may be, geographically, the closest spine surgeon to the FDA. No one is paying my travel expenses. I live 10

minutes from here. However, the price of gasoline these days I might have to rethink it in the future.

I have a keen interest in research. I serve as an Assistant Professor of Orthopedic Surgery at Howard University and have been involved in numerous IDE studies, both as an investigator and as a data safety monitor officer.

I am here today because I am representing the North American Spine Society, the largest spine organization in America. The 3,000 members actually up to 4,000 members now that we have share similar interests as I do; that is, patient care, research, and education.

NASS is comprised of both surgeons and non-surgeons, representing the various fields of spinal care, including orthopaedic surgery, neurosurgery, psychiatry, radiology, and anesthesiology. Our members have one primary interest: to provide the very best quality medical care to our patients. The end result should be less pain and better function, resulting in a better quality of life for our patients.

Like you, we recognize that the landscape of spinal care is rapidly changing. Consequently, the way we study spinal care may need to also change. From reading your four proposed questions, it is clear that you already appreciate this.

Regarding your first question about time to intervention, this will depend on patient pathology. However, since the devices you are inquiring about are designed for earlier intervention, the time to intervention may logically occur at an earlier time in the disease process.

For example, six months of non-operative treatment may be reasonable before a spinal fusion, but may be too long for one of the less invasive procedures being discussed today. Degenerative disc disease represents a wide spectrum of intradiscal disorders, and each stage needs to be specifically addressed. Different levels of disease require differing approaches to conservative treatment.

Your second question about controls is something that I think about a lot. Fusion, as a control in a randomized study, may not be the best

model when investigating these less intrusive devices. There are several reasons for this.

Firstly, fusion may be a much more aggressive treatment than is warranted for the pathology being studied. This has some ethical concerns. Secondly, these devices can be used for differing levels of degenerative disc disease, and the controls may need to be different for various disease states. And, thirdly, the goal of treatment is not to ankylose the spine. The goal is to provide a stable platform that allows motion. Fusion is the antithesis of this.

The North American Spine Society is committed to the application of evidence-based medicine evaluation to both the current practice of operative and non-operative spine care as well as the evaluation of new technology.

Although well-designed, prospective, randomized, blinded studies are most helpful in drawing conclusions when comparing treatments, it remains important that all of the scientific evidence is critically examined, including other levels of

evidence. Despite the limitations and greater influence of bias and confounding factors in such studies, these still provide information which should also be given consideration.

Since the devices we are talking about today are not for fusion, but are for motion preservation, endpoints (your third question) will likely occur sooner than the traditional 24 months used in fusion studies. When you think about it intuitively, motion preservation occurs immediately, whereas with fusions, it is a lengthy process.

Endpoints need to be flexible depending on the device being studied and the level of disease being treated. Some devices may require only short follow-up, and some devices may require very long follow-up depending on the control being used. It may also be instructive to shorten the follow-up on motion-sparing devices, while still rigorously following the patients in a post-market environment. Again, endpoints should not be set in stone. Pain relief is the goal.

Finally, your fourth question has to do

with changes in study design for mild to moderate disc disease. With earlier intervention for lesser disease, smaller changes in outcome scores would be inevitable and expected. This needs to be accounted for.

A 15-point drop in Oswestry score may be impossible, while a 15 percent drop may be more realistic. A percentage drop from pre-op screening would make sense. While Oswestry is a good assessment tool, others can also be valuable. This includes VAS, SF-36, and the NASS Outcome Assessment Tool.

With regards to increasing the delta value over 10 percent, this certainly may be appropriate depending on the control being used. A higher delta value would allow more studies to proceed because of easier recruitment abilities.

The North American Spine Society applauds you in your attempts to improve on the design and process of spine research in the United States. Our goal as an organization is to provide the very best care to our patients. This may mean intervening in their disease process at an earlier stage in different

ways.

The North American Spine Society would like to sincerely offer its assistance to FDA in any way we can. We are prepared to provide experts in different fields of spine care to work with you on developing specific protocols, outcome tools, controls, etc. for the spectrum of conditions within degenerative disc disease. Thank you very much.

DR. NAIDU: Thank you, Dr. Schneider.

Next representing St. Francis Medical Technologies is Dr. Paul Anderson of the University of Wisconsin.

Dr. Anderson.

DR. ANDERSON: Good welcome. I welcome the opportunity to address the panel. I am a board certified orthopedic surgeon and associate professor of orthopedics and neurological surgery at the University of Wisconsin. I am a consultant to St. Francis Medical who paid my travel expenses and electronic.

The questions that the panel has been asked to address relate to devices intended to treat

lumbar degenerative disc disease in patients with mild to moderate "back pain." Back pain may be the primary complaint in patients with isolated disc involvement.

However, in the case of degenerative conditions such as spinal stenosis, patients may experience back and leg pain. These are important distinctions the panel needs to take into consideration while debating such issues as study entry criteria and study endpoints based on device type.

Also, the appropriate use of clearly defined terminology in clinical trial design is an of paramount importance and too often overlooked. The unintentional misuse of terms such as success and failure can dramatically impact the interpretation of study outcomes and present issues as "black and white" when, in reality they frequently are not when patients are concerned, as I will attempt to illustrate.

I would like to comment today on several issues that are fundamental to the panel's discussion and must be considered when determining the structure of clinical trials for these types of patients. These

issues include:

The definitions of success and failure in clinical trial design.

The selection of the appropriate control group that allows for valid, quantitative comparison to the treatment group.

The selection of valid study endpoints in patients with mild to moderate symptoms.

Defining "success" and "failure" in patients with mild to moderate symptoms is open to much debate in the research community. Until we agree on definitions that are both clinically reasonable and scientifically valid, we have no solid foundation upon which to judge the effectiveness of devices in this patient population. Secondly, the definition of a clinically significant response to treatment in patients with mild to moderate symptoms is fundamental to determining success and deserves equal attention.

In 20 years of treating patients with spinal disorders and involved in numerous clinical trials, I have found that patients consider surgery because they have significant impairment in their

quality of life and have weighed the possible benefits against the risks. This is a highly personal choice for the patient.

Some patients are willing to undergo a less invasive procedure but will not undergo a major procedure even if it offers a chance of higher success. Other patients view the risks of any surgical intervention as too great and would be satisfied with some level of improvement by continuing with non-operative therapy. Is it appropriate to consider this patient a failure if the patient is satisfied with this outcome within the context of his or her choice of treatment? Probably not.

We all know that patients must undergo a minimum amount of non-operative therapy before we consider a more invasive procedure. This does not mean that a patient has "'failed" nonoperative therapy at some arbitrary time point if the elects to continue with this therapy. The only certain failure point is the patient's decision to abandon nonoperative care and undergo surgery.

Unlike patients with herniated disks and

discogenic low back pain where there are well established guidelines for timing of intervention, with patients with lumbar spinal stenosis there is no established length of time to surgery.

Is it appropriate to use the same criteria for determining a successful outcome in a patient treated nonoperatively, to a patient who has elected to undergo a major procedure like a spine fusion? No. The patient who elects to undergo an invasive procedure has the reasonable expectation of more than just a small degree of improvement.

In measuring outcomes the most important metric is the patient's satisfaction with his outcome in the context of his treatment. Patient-reported outcomes measures are now a mainstay in clinical research and include general health, disease-specific outcomes and patient satisfaction.

The weakness of most of these is the absence of valid measurements of what constitutes a clinical difference, especially in patients with mild to moderate symptoms.

Outcomes research experts are now

incorporating a patient's satisfaction with treatment or a patient's assessment of whether the treatment helped as a yardstick for determining a successful outcome.

As Walsh and colleagues noted in their recent paper on the responsiveness of the ODI, MODEMS and SF-36 outcomes measures, "While there is no gold standard to measure an actual change, it is difficult to argue that no improvement has occurred if both the patient and clinician independently and simultaneously report improvement."

The authors therefore used the patient's perceived improvement as the criterion to measure the sensitivity and specificity of these outcomes measures and have established satisfaction as a gold standard.

So how do we determine clinical success in patients with mild to moderate symptoms? The consensus among outcomes experts is that the "minimum clinically important difference" or "MCID" is the appropriate standard to define clinical success. This standard is particularly relevant when applied to patients with mild to moderate symptoms where the risk

of false negatives is significant due to "ceiling" effects that may occur when less severe disease states are being evaluated.

Clinically significant levels of improvement need be defined and should not be chosen arbitrarily. An absolute 15 point change from baseline in the ODI score at two-year follow-up was chosen by FDA for back pain studies as clinically significant and is now accepted as the "conventional" standard to define clinical success.

In my review of the literature I find only one article, by Mannion and colleagues, in which the minimum clinically important difference is validated for the ODI. It turns out the authors determined a "good outcome" is defined by a cut-off value of 11 points using ROC analysis, not 15 points, and the minimum clinically important difference for an individual patient is 9 points.

This validation was based not on 2-year data, but 6-month data. The authors of this paper, which include Jeremy Fairbank who developed the ODI, also recommend a percent change from baseline rather

than absolute amount of improvement for consideration. They further acknowledge that the cutoff value for patients treated conservatively may range from 4 to 6 points, much lower than the 11 points for patients treated operatively.

Finally, the ODI has been reported to be more sensitive in detecting change in patients with more severe disability and less sensitive in detecting change in patients with mild to moderate disability. Based on careful review of the literature, there is no evidence that a 15-point change from baseline in the ODI score is a scientifically valid measure of the minimum clinically important difference in patients with mild to moderate symptoms.

Therefore, I believe it is imperative that we validate the appropriate thresholds of clinical significance that we use to define success in an individual patient. There are outcomes measures in which thresholds for improvement were determined as part of the clinical study validating the instrument, thus providing guidance for how to interpret outcomes. For example, in patients with spinal stenosis, the

Zurich Claudication Questionnaire has statistically validated values for clinically significant improvement.

Next, we need to take into account the large difference in risk profiles between current operative treatment and non-operative therapy. This makes the dilemma for patients with mild and moderate symptoms especially difficult. And this is why the advent of new devices and procedures, which offer the possibility of improving outcomes without adding to, or possibly lessening surgical risk, important and desired by patients.

In designing the clinical trials to evaluate new devices, the dilemma for investigators is choosing the appropriate control therapy. The consensus of the clinical literature on degenerative lumbar spinal stenosis is clear that nonoperative therapy is the standard of care for patients with mild to moderate symptoms.

From an ethical standpoint, it may not be appropriate to randomly assign a patient with mild to moderate symptoms to an invasive and risky surgical

procedure when good outcomes are not well established and the risk-benefit ratio may not be in the patient's best interest.

Patients with degenerative lumbar spinal stenosis are elderly and may have medical comorbidities that increase the risks of surgery and diminish efficacy. Ethically, you must select investigational and control therapies that have the potential to offer comparable risk profiles benefit. For the at-risk elderly population in particular, nonoperative care is a particularly appropriate control for minimally invasive investigational procedures.

Nonoperative care is a particularly appropriate control for interspinous spacers since neither treatment exposes patients to the risks of neural injuries and general anesthesia, and future treatment options remain open should they be necessary. On the other hand, interbody fusion was the appropriate control for artificial disc studies, since both treatments expose the patient to a similar level of risk.

In conclusion, I believe the clinical studies we undertake to evaluate devices must take into account:

(1) The risks and benefits of any therapy have to be balanced and considered when selecting appropriate control groups for clinical trials of new therapies.

(2) The terminology used to define success and failure, study endpoints, and other critical elements of a well-designed study protocol must be clearly and consistently applied for each patient population.

(3) A patient's level of satisfaction with his treatment is the most clinically meaningful measure of treatment response and provides a valid basis to determine thresholds when defining a successful response to treatment.

(4) The strengths and limitations of outcome instruments must be recognized in order to select clinically significant endpoints that match the patient disease state and demographics and the types of devices under study.

I would like to thank you for this opportunity to address the panel.

DR. NAIDU: Thank you, Dr. Anderson.

The last speaker for this open public session will be Dr. Stephen Hochschuler representing the Spine Arthroplasty Society. He is the 1st Vice President of the Society.

Dr. Hochschuler.

DR. HOCHSCHULER: Thank you. Good morning. My name is Stephen Hochschuler. I am a board certified orthopedic surgeon practicing spinal surgery. I am a member of the AAOS, ISSLS, NASS and co-founder and Chairman of The Texas Back Institute. I am here today as a founding board member and 1st Vice-President of the Spine Arthroplasty Society.

I have come to this hearing to help address issues relating to Spinal Arthroplasty. Spinal surgery has changed over the past several years from stabilization associated with fusion to stabilization via motion preservation.

With this evolution it has become evident from the FDA posed questions to be discussed today, as

well as concerns voiced by practicing spine surgeons and patients, that there needs to be a reconsideration of FDA approved clinical studies. Do the study protocols of yesterday apply today? Do the requisite needs of safety and efficacy merit the cost of the study?

For example, is it possible to utilize computer modeling and previous controlled double blind studies analyzing historical data from one arm of such study to compare to a new device in a stand alone trial? I believe it's time to rethink the entire analytical process to expedite the development of new technologies while protecting our patients.

Over the past several years, largely due to the Internet, patients have become more enlightened and empowered as to their medical decisions. It is not only important to consider what we as scientists and clinicians hold important but also what our patients value.

Is prolonged pain and suffering associated with the inability to work and partake in one's social environment while undergoing "Conservative Care"

merited? Is a minimally invasive, minimally destructive, reversible operative procedure less conservative than our traditional definition of conservative care?

We in the USA have prided ourselves in delivering the best medical care in the World. Nevertheless, our citizens more and more utilize non-FDA alternative medical therapies. Why is this? Is our approval process part of the problem?

The Spine Arthroplasty Society was founded approximately five years ago. At the time I had a particularly ethnocentric opinion that outside the USA studies were inferior. Since, I have learned that although they might not be perfect, the data is worth considering and the CE Mark process as well.

Today, The FDA has elected to evaluate how studies should be organized to determine the safety and efficacy of nuclear replacements, interspinous process devices, and pedicle screw based dynamic stabilization systems. All three technologies are key to the development of spine stabilization surgeries associated with maintenance of spinal motion.

Questions that have arisen and need to be addressed include:

(1) Is the proposed device considered minimally invasive, minimally destructive and readily reversible or salvaged? These types of devices will be justified earlier in the continuum of care. The traditional six months of failed conservative care prior to surgery is likely to compromise the potential efficacy of these devices and the low risk and preservation of options justify earlier use. One possible explanation for the relatively low success rates of fusion/arthroplasty may be that we wait to long to intervene.

(2) Does the proposed devise have the potential to prevent the degenerative cascade as described by Dr. Kirkaldy-Willis? Early intervention could have long term benefits. Once the cascade has resulted in loss of disc height, chronic muscle spasm and facet disease, surgery is much less likely to be successful.

(3) Is six weeks to three months of incapacitating low back pain as defined by the Visual

Analog Scale, Oswestry Index, etc., enough to merit surgical intervention? It depends on the nature of the surgery and the risk profile of the device. If a product is minimally invasive and doesn't burn bridges, then earlier use should be considered.

(4) Is continued conservative care after three months more intrusive to a patient's well being than a minimally invasive, reversible procedure? It becomes unethical to prohibit a patient from surgical care if they aren't responding to conservative management alone.

These patients must be told when they enroll into a conservative care study that if they don't respond to it, then they can pursue surgery and still be in the study.

(5) Would an early, minimally invasive, motion preservation surgical intervention save the patient the grief of being unemployed with all the concomitant family, social and financial issues?

Again, early intervention with these types of devices may break the degenerative cascade and get patients back to work sooner. We know from numerous

studies that the longer someone is incapacitated with back pain, the less likely they are to make full recovery. Early intervention allows them to rehabilitate that much sooner.

(6) The cost of a worker's compensation low back claim is substantial. The indirect costs are noted to be three times the direct costs. Would the device under consideration allow an earlier return to work and save society a significant financial burden? Very possibly yes.

(7) Last, and perhaps most important, what criteria are our patients most interested in after safety and efficacy issues are addressed.

(a) Relief of Pain.

(b) Return to Function to include: Work, Leisure Time, Sleep and Sex.

(c) Prevention of downstream degeneration associated with the potential exacerbation of pain and disability.

Patients don't want to hurt anymore; they want to live their lines. I recognize that as a representative of The Spine Arthroplasty Society, I

have made a statement rather than address the specific FDA questions posed. Obviously we do not have all the answers today, but this meeting is a good start.

My main concern is that practical, cost saving, expeditious decisions are made without compromising the safety of our patients. Thank you for allowing me this audience.

DR. NAIDU: Thank you, Dr. Hochschuler.

This will conclude the open public session. We will take a 10-minute break. We will reconvene at 9:45.

(Whereupon, at 9:37 a.m. off the record until 9:56 a.m.)

DR. NAIDU: It's almost 10:00. I would like to call this meeting back to order. Before we proceed with the FDA presentation, is there anybody else in the public that would like to address the panel at this point? If so, please come forward. State your name and affiliation.

Before we proceed further, Ms. Adams, would you please introduce yourself?

MS. ADAMS: Good morning. I'm Pamela

Adams. I'm with Etex Corporation and I'm the industry representative to the panel.

DR. NAIDU: Thank you, Ms. Adams. At this point we will proceed with the FDA presentations on this topic. The FDA presenter is Mr. Jonathan Peck.

Mr. Jonathan Peck.

MR. PECK: Thank you. Good morning. My name is Jonathan Peck. I'm a reviewer in the Orthopedic Devices Branch in the Office of Device Evaluation. I would like to take this opportunity to thank the members of the panel for being here today to help FDA out with our questions on this topic.

I would also like to thank the presenters this morning. The information you shared is essential to a productive discussion this afternoon.

I would like to give a special thanks to two of my colleagues, Dr. Kristen Mills and Mr. Justin Eggleton for all their hard work and help in preparing for this meeting.

Today we will be discussing clinical trial design for devices intended to treat mild to moderate lumbar degenerative disease. I'll start out with some

brief background information and then I'll move into discussion of issues related to intended study population, potential control groups, and study endpoints to these clinical trials.

Finally, I'll present FDA's questions to the panel.

It is estimated that 60 to 80 percent of the adult population will experience low back pain at sometime in their lives with up to 5 percent experiencing this pain on a yearly basis. Chronic low back pain is one of the most common reasons for physician visits in the United States. It's one of the leading causes of employee absenteeism and disability. It accounts for relatively large percentage of all U.S. healthcare expenditures.

The causes of low back pain are multifactorial and the specific pain generator typically cannot be isolated. Normal aging of the lumbar spine involves a sequence of degenerative changes that likely start at a biochemical and cellular level and then turn into the changes that we see clinically.

The functional spine unit is made up of the intervertebral discs, the two facet joints, the ligamentous structures, and the retrieval bodies. Each component of this complex undergoes changes of aging and degeneration.

It's hard to know what a bulging or degenerated disc means clinically as was shown in the study by Boden. As you can see, the majority of patients over the age of 60 that Boden looked at show some radiographic signs of disc disease without showing any symptoms.

Now I'll discuss the continuum of treatment options. The vast majority of patients with low back pain are successfully managed nonoperatively. A wide variety of nonoperative treatments are available including physical therapy, medications, and injections. Probably there is really no set treatment protocol.

On the other side of the spectrum, if symptoms persist or progress despite nonoperative management, surgery becomes an option. Extended care for most patients for whom surgery has been deemed

necessary has been spinal fusion and/or decompressive procedure. Total disc replacement has become a more recent option.

Over time less invasive procedures have been developed to treat disc herniation and more minimally invasive approaches for laminectomy and spinal fusion have evolved.

I just want to clarify that this treatment continuum was meant to organize treatments based on the level of invasiveness and it does not necessarily directly correlate with the disease continuum.

Recently new devices have been reported in the literature that fits somewhere in between nonoperative care and more invasive surgical options. You have heard about a number of these devices in earlier presentations and read about several of them in the literature provided in the panel pack.

Some of these new devices has been produced for use in patients who based on current surgical options would have been treated with nonoperative care.

These new devices are all intended to

stabilize the affected functional spine unit while maintaining some degree of motion. These devices are quite variable in design, function, and region of implantation so we have broken them out into three design categories for your consideration.

The first group consist of spacers between adjacent spine processes. The second group is nucleus replacements and the third group is systems that are pedicle screw based.

Currently there are several parameters that FDA is relatively comfortable with to determine patient inclusion for lumbar spinal studies. For example, we typically like to see that a patient receive six months of nonoperative care prior to inclusion.

With regard to baseline pain and function levels, for example when using the Oswestry disability index we prefer baseline score 40 but have accepted 30 within appropriate rationale. We are also relatively comfortable with the radiographic findings we suspect to see for inclusion.

With regard to the new devices it may make

sense to alter some of these inclusion parameters to capture patients that fall earlier in the disease continuum. This is something we are going to ask you to discuss.

Before moving into our main discussion, I just want to outline the main topics that our questions will be centered around. We will be asking you about intended patient population, potential control groups, appropriate study endpoints, and miscellaneous questions about study design.

Many patients suffering from more mild to moderate disease may not be ideal surgical candidates who warrant treatment with a permanent spinal implant. The associated risks may not be appropriate for patients with mild to moderate disease and the benefits may not last long enough to have warranted to the intervention. The question will be for these type of devices how do we define the patients to study?

There are multiple control options for these studies. One such option is nonoperative care control. These control arms are designed to include various combinations of medications, physical therapy,

patient education, and injections.

An additional option for nonoperative care control is a crossover or secondary treatment design which is also referred to as a rescue procedure in the earlier presentations.

The other control option would be surgery in the form of fusion, total disc replacement, laminectomy, etc.

FDA see potential limitations with both nonoperative and surgical control options. If a patient has exhausted nonoperative care options, then it may not be appropriate to randomize that patient to receive nonoperative care and it could lead to a low success rate in the control group.

On the other hand, if patients are not allowed to exhaust nonoperative options, any outcomes observed during the trial may not be due to the device. In addition, it may not be ethical to treat patients with mild disease with a implanted device.

Also, compared to surgical intervention nonoperative care introduces potentially significant bias due to placebo facts. On the other hand, considering surgical control option, patients with

mild to moderate disease do not necessarily meet the criteria established for fusion, disc replacement, laminectomy, etc.

We have concerns about randomizing these patients to an invasive procedure that they might not need. In addition, regarding the crossover and secondary treatment designs, we aren't sure how to objectively define when a subsequent intervention is warranted so we will be asking you to discuss appropriate control group options.

Traditionally, studies of spinal devices compared some or all of the following endpoints at the 24-month time point. Pain and function scores, quality of life assessments, radiographic evidence of fusion or motion, adverse events including secondary surgical procedures, and neurological assessments.

A number of pain and function assessments, for example, the Visual Analog Scale and the Oswestry Index have become commonly accepted as endpoints in clinical trials. These traditional spinal study endpoints may not be the most appropriate endpoints to evaluate patient's mild to moderate disease at

baseline.

With regard to pain and function assessments, the ceiling effect may come into play given the potentially lower baseline scores. FDA believes it is important for these studies to show durability in response to the device. We are concerned that the subjective nature of the pain and function assessments may not capture the true treatment affect. We will be asking you what the most appropriate clinically significant endpoints are for these studies.

FDA's concern with study design is it does not demonstrate a mechanism of action. Some proposed mechanisms of action are the device may delay or halt the progression of DDD. The device may maintain or restore disc type. Device may increase canal frame dimensions or the device may delay or eliminate the need for more invasive surgical options while providing equivalent results.

FDA believes demonstrating a mechanism of action may be valuable, especially patients suffering from mild to moderate disease are studied and

conservative care is used as a control.

That's the end of the FDA presentation. Would it be helpful for me to go over the questions now or should we wait until later?

DR. NAIDU: Why don't we just go over the questions briefly so that we have an idea as to what to address.

MR. PECK: Okay. Now, when considering the questions, please consider that you may have different conclusions for each of the three device types listed and the two disease states listed as well. When formulating your response, please clarify whether the answer is specific to either device type, disease state or if your answer is more general.

Here are the main topics the questions are based on.

Question No. 1, Intended Population. Considering the natural history of lumbar degenerative disease, please discuss appropriate time to intervene with a permanently implanted device intended to treat mild to moderate disease. Then please discuss the characteristics that should be used to define

appropriate candidates for a clinical study.

At a minimum, please consider the type and amount of nonoperative care a patient should receive prior to inclusion and specific baseline criteria (e.g., ODI, VAS, neurologic findings, radiographic criteria) that patients should meet prior to inclusion in a spinal device clinical trial.

Question No. 2, Control Groups. Based on the population of appropriate surgical candidates discussed in Question No. 1, please discuss the control options, nonoperative or operative, for each of these device type. Please consider that a clinical study must be designed to demonstrate a treatment effect.

For example, it must be designed to show that any observed clinical outcome is due to the device rather than other confounding factors and treatments. When considering this issue, please consider the following dilemma. On one hand, in order to warrant surgical intervention patients may have results to nonoperative therapy options.

However, on the other hand, a patient

should not be randomized to a control treatment that they have already "failed."

Also, remember that these patients may not meet the currently used criteria for surgical intervention. Please comment on the use of "crossover" and secondary treatment designs. Specifically, please comment on how to define patients who have "failed" the first treatment and thus are eligible to go on to the second treatment.

Question 3, Endpoints. Please discuss the most appropriate clinically significant endpoints to evaluate subjects with mild to moderate lumbar degenerative disease. Please discuss what value, if any, there is in demonstrating a faster response as opposed to comparing responses at the final study evaluation time point, which has traditionally been 24 months.

If demonstrating a faster response is considered important, please discuss the length of time the response should last to consider the device a success. Please also discuss the value of potential mechanism of action endpoints. Which of

the proposed endpoints might the sponsor be able to demonstrate and how.

For example, should restoration of disc height and hydration be shown through objective radiographic criteria? Finally, please discuss the endpoints for demonstrating if earlier intervention is warranted because it alters or delays the course of the disease.

Our final question has to do with Study Design. Please discuss what changes to traditional spinal device study designs might be appropriate given the less invasive nature of many of these devices as well as the mild to moderately affected patient population. Please discuss the appropriate final time point to evaluate study endpoints to make a determination of study success.

Please discuss whether it is appropriate to define a small change in pain and function scores as clinically significant given that these devices may pose less risk and that the inclusion criterion score may be lower and the ceiling effect may come into play.

Depending on the study control, please discuss noninferiority versus superiority. Also, please discuss whether an increased delta may be appropriate depending on the control.

DR. NAIDU: Thank you, Mr. Peck. If you could go back and post the first question up before I introduce the panel. We will now begin the panel discussion. Dr. Michael Yaszemski will open this part of the meeting with his remarks to help us focus.

Yes, Mr. Melkerson.

MR. MELKERSON: Just one point of clarification. In the description that we've described of different device types, it was brought up in the presentation that it should be based upon the claims. It should be pointed out that the device types we have listed have made various claims associated with their design so when you are addressing the questions you can either approach it from device by device or by the claims associated with that device because of those three device types were identified we have various claims made for each of the three device types.

DR. NAIDU: Thank you, Mr. Melkerson.

Dr. Yaszemski.

DR. YASZEMSKI: Thanks, Dr. Naidu. I would like to make an introduction to the panel discussion that we are about to have. I think that as part of that discussion I'm going to start with my conclusion so we can go from there. My conclusion is that it's not appropriate at this time to provide strict answers to any of these questions.

I think we're too early in the evaluation of these types of devices to make any global statements that will then bind either physicians or patients or device manufacturers into a narrow pathway.

I think what it is appropriate to do is to provide our thoughts together with our clinical and industry colleagues as to a framework for evaluation of each device that comes down the line, the questions to ask for each device and each patient inclusion group that will then get to these four questions that we'll discuss today.

That's going to be the gist of what I have

to say. I think that the over-arching criterion that we should look for is equipoise for each patient. When Dr. Blumenstein talked before, he talked about the time of randomization and the decisions to be made.

I think for each individual patient when a physician and a patient are together and making that decision to randomize, at that point the two choices available must be equal in their risks and benefits to the patient to the best of our knowledge.

I think that as we answer these questions specifically, we should be trying to get to that point. Are we presenting patients with, as best as we can tell, equal options whether we choose the control or the study for whatever device is under consideration at the time.

To get to that, to get to equipoise at the time of randomization, I think that there are two issues from which our discussion of the questions will flow. They are, No. 1, clinically appropriate care and, No. 2, scientific validity, in that order. I think that the clinically appropriate care gets to the

equipoise. Each patient that comes here to think about one of these devices there are three classes of devices and several classes of disease processes.

Depending upon the mix of the disease process the particular patient's position along the path of that disease process, where they are stage wise, and the device under consideration, each of those mixes is going to be different for each device and each set of inclusion criteria for the studies that are proposed.

With scientific validity when we do get to the study it will be less than ideal if after the study is done and the data are looked at that they are not valid to the point that we can make scientific conclusions so I think that we need to keep those things in mind as we deliberate. Is the care appropriate and are the data going to be scientifically valid?

Let me look next at just two examples to say why I think that this group is heterogeneous enough that we can't provide anywhere near firm or rigid guidelines. The disease process

and its natural history, the anticipated clinical path, are going to be different whether the person is -- the two examples I'm going to use are a young person previously asymptomatic who has had some event and has a combination of back and leg pain, the typical herniated disk person, early in the disease process. The second, a person who has degenerative spondylolisthesis and spinal stenosis who has been going along and is less and less able to get through his or her activities of daily living. I think that these two somewhat extremes demonstrate the heterogeneity of the patient groups and how we will have to apply the conditions of equipoise in these varying situations.

The disease, that is one. Then the second -- excuse me. That discussion will be focusing on the disease process. The second will be on the device itself. Each of these devices has different risk benefits. There is a different surgical risk depending upon, as we've heard many of the presenters this morning, whether it's minimally invasive or traditional surgical procedure.

These devices span that spectrum. There is a different anesthetic risk. Some of them can be put in under local anesthesia and some of them require general anesthesia. The reversibility I think is also important because that reversibility includes two things from what I've heard this morning and from what I've read.

That is, what existing anatomy is altered when putting the device in that will stay altered when you take the device out and how do you have to take this device out. As we've heard this morning, some of the interprocess spacer devices will be different to take out, for example, than a prosthetic nucleus, a noninjectable prosthetic nucleus.

Now, the examples again that I gave I would like to give to just frame out subsequent discussion here. I would like to give two examples where I think the answers to the questions will be widely different.

First, let's look at that 21-year-old patient who has had his or her first episode of pain and has a herniated disk, back and leg pain. The leg

pain is getting a little better. Back still hurts four weeks out. We ask the question is six weeks of treatment long enough after which we invoke some device.

Let's look at the other patient. She's a 70-year-old person with degenerative spondylolisthesis and spinal stenosis. She has neurogenic claudication. She has had it for a while. She has gone through a number of nonoperative treatments. She has had a couple of injections. They have lasted for a while. The extent of her relief is getting slower and slower. You see her at this time and then ask is four more weeks or six more weeks of treatment enough.

I would propose to you that the answer to is six weeks enough very different for both those patients. I would propose that in the first case. It's not appropriate to go to any minimally invasive procedure. In the second case it might be.

Now, let's look at devices. Pedicle-based systems, interspinous spacers, and prosthetic disc nucleus, both injectable and implantable. The pedicle screw based systems can be put in percutaneous or

open. The questions I might ask when asking the risk benefit analysis for them, if they are open or percutaneous we may have to retract the muscles to put them in.

If we retract the paraspondis muscles how long is it going to take to do so. The risk, although it's minimal in experienced hands, there always is some risk to vascular or neurologic structures putting a pedicle screw in. They can be removed. They can be removed percutaneously or they can be removed open.

Let's look at the interspinous spacers. They can be put in under a local anesthetic. The risk to nervous and vascular structures, as we've heard this morning, is very small and they can be removed with very little alteration to the normal anatomy.

Let's look at the prosthetic fixed disc nuclei. If the PDN is an injectable PDN and the study under consideration is one in which a discectomy is already being done, the risk of surgery and anesthetic that has already been made. That decision has already been made. They are taking care of the patient. This study might be having the PDN during surgery.

If, however, it's a degenerative disc disease patient who is not otherwise getting an operation, that same injectable PDN has to undergo different scrutiny than it does in a case where a surgeon has already elected to proceed with the decompression.

If the PDN is not injectable but implantable and has to go in either posteriorly or anteriorly, this presents a different situation than the injectable PDN. I say these things not to get us to an answer but to emphasis the great heterogeneity in the patient population and of devices that has to be considered each time a device proposal comes in front of the FDA.

Again, I'll restate my conclusion. We are too early, I think, in the assessment of these devices to make any rigid criteria. I think that a matrix of considering the specific disease, the inclusion criteria for the patients proposed for a study is going to result in an appropriate decision on the answer to these four questions.

Then with time since it's quite apparent

that these devices are going to continue to come for approval and for patient use, I think patterns will emerge that will allow firmer answers for the four questions. Thanks, Dr. Naidu.

DR. NAIDU: Thank you, Dr. Yaszemski. Let's just go on straight to the panel questions at this point. The questions are fairly detailed, I think. This will lead us to the discussion as well.

I would like to start off with Dr. Kim. Dr. Kim, if you could address the first question that's posed to us with respect to the nuclear replacement devices, the spacers, and the pedicle screw system. For each if you could outline your opinion, I would appreciate it.

DR. KIM: First of all, I want to echo Dr. Yaszemski's comments that there is such a wide variety of implants and diseases and various combinations that it's probably too early to make any specific recommendations or requirements.

I would say that I agree with virtually everybody that has made a presentation today that a standard six-month number of preoperative or

pretreatment trial of conservative therapy is probably not a number that we should be relying on. It makes sense for certain disease types but for some of these other disease entities and implants that may be too long, or it may be too short.

A general guideline, I think, is important because it decreases the uncertainty that the study sponsors and the investigators face whenever they come to these PMA meetings so I think it would be beneficial to have some type of guidelines. I don't have any specific numbers but things like herniated disc it doesn't seem reasonable to have to wait six months with nonoperative treatment because that is not how we take care of these patients in our clinics. That would be something that may benefit from a shorter nonoperative treatment time period.

On the other end of the spectrum is something like lumbar stenosis. We know that is a very slow gradual process and six months seems very reasonable. In some cases depending on the implant we may want to recommend even longer times although six months seems reasonable.

I just want to echo what people have said that the FDA needs to be a little bit more flexible in making certain requirements and especially now where all the spinal implant devices are so different than what we have been looking at. We need to really work together with the study sponsors to come to some agreements almost on a case-by-case basis.

If I have to try to make some generalizations for nucleus replacement devices, that's a hard one because the two indications that I see is to replace the nucleus after a discectomy so if you are treating somebody for a herniated disk, waiting six months doesn't seem reasonable.

But if you are treating somebody with a nucleus replacement device for low back pain, waiting six weeks doesn't seem reasonable. Low back pain is a difficult entity to describe in the first place in terms of its natural history so something like that waiting six months would be reasonable so it would depend on what the study sponsor claims the purpose of this device will be for.

Interspinous process spacers tend to be

for stenosis patients so the six-week period is not reasonable and six-month period would be more reasonable. Then, finally, the pedicle screw dynamic stabilizers again depends on the disease entity that they are proposing to treat in the particular PMA. I would go by the same guidelines that things like a herniated disk doesn't have to wait six months but a treatment for low back pain or stenosis would need to wait longer.

DR. NAIDU: Thank you, Dr. Kim.

Dr. Diaz.

DR. DIAZ: As I was flying here, I was trying to figure out what would be a sensible way to make a rational decision and a rational comment about how to deal with this very complex problem. I think Dr. Yaszemski put it out very clearly that we are not dealing with a homogeneous population. This is a very heterogeneous population at best.

Not only is a heterogeneous in a sense of scope of disease but in quality of manifestations and type of individuals that it presents on. I cannot envision how we can come up with one solution that

fits all with this approach that we are asked to take today.

I don't think we can provide you with a single recipe for a solution that will address all the questions that not only the patient population presents, the clinical manifestations have, or the devices are used to treat these problems are really giving us an opportunity to participate in the case of these patients. I believe that the only way that we can provide a sensible answer is addressing each and every one of the problems individually.

I believe that if we are talking about the young individual who has been a rugby player, as I heard this morning in the elevator, who has been beating his brains against somebody else's knees for months and comes in with back pain and may have an acutely ruptured disc is going to have the same possible solution as grandma who has been gradually deteriorating over the last 10 years.

She has had manifestations that even though subtle are real but have not been terribly incapacitating to her to the point where she has been

able to function reasonably well, although gradually losing ground and eventually coming to see us because we don't have a solution to her problem.

Coming up with a study time to decide when to intervene on these patients I think has to be individualized. The young athlete that has an acute sprain in the back and may have nothing other than myofascial pain even though we treat that patient for six weeks and we say there are MRI changes that show that there may be an annular tear, if it were me after I played football and I had an injury like that, I know I got better with not doing anything and I have been able to continue to do well for many years.

I don't think that there is a real solution to the time dilemma that this question presents and to try to come up with a broad answer to be all inclusive for all of these devices and all of these problems I think is asking too much.

DR. NAIDU: Thank you, Dr. Dias.

Dr. Rudicel.

DR. RUDICEL: I think I would agree with what everyone else on the panel has said. I guess I

would like to add that I think with these complex problems that we have to think outside the box. For example, I don't think a randomized trial, while it is certainly the gold standard but that may not always be the answer for how to deal with these issues and how to conduct a study so I think we have to think in different ways of dealing with this and certainly dividing up the patient population each device has something different that we are trying to treat.

I think it's difficult to compare conservative treatment with surgical treatment. I think looking at different study designs for doing that can be quite helpful.

Also, I think we do have some historical controls for these different problems that can be of benefit.

We do have a lot of information for the natural course of disease in some of these problems and I don't think we want to ignore that. I would agree with the panel that it is a myriad of problems and we can't come up with one solution for that.

DR. NAIDU: Thank you, Dr. Rudicel.

Ms. Whittington.

MS. WHITTINGTON: I agree with the comments from the other panel members in that these patients certainly have different diseases and different problems that need to be addressed in different ways.

As I sit and listen, I think it's also important that we consider that many of the patients that the surgeons are seeing have already been exposed to a period of conservative treatment by their primary care physician or practitioner and that discounting that and looking at research that's done would potentially be inappropriate as well because of the delay of treatment to patients who would benefit from earlier treatment.

There was also discussion about guidelines that may already be available for evaluating or timing treatments from the American Academy of Orthopedic Surgeons so taking that into consideration would also be important when the panel decides or evaluates research that's submitted by different companies.

DR. NAIDU: Thank you, Ms. Whittington.

Ms. Adams.

MS. ADAMS: My comments are offered from an industry perspective but I would say that I agree with most of the panel members about the issues of heterogeneity that we are struggling with here. From an industry standpoint we are helped by FDA issuance of guidance documents.

We rely on them, we look to them, we try to follow them, and they are useful to us. I'm a little concerned that this may not be the appropriate approach for these types of devices and it may be too early to be thinking about setting standards for such a large range of devices, disease cases, patients, etc.

The other thing I would just like to say is that from an industry standpoint I think we rely really heavily on clinicians and the physicians that we work with as investigators to give us their ideas about standard of care, about times to intervene, about what the appropriate endpoints might be.

I think that in this early stage with these types of devices that may still be the best

approach. We are as an industry a little uncomfortable about thinking about regulatory answers to these sorts of things just because there is so much that we still need to learn from clinicians and there is so much information that we need to rely on from principal investigators.

As tricky as it is and as much as it may not be the answer that would be useful to the FDA, I really think that this is a very difficult thing for us to give one size fits all.

DR. NAIDU: Thank you. Can I give my comments?

MR. MELKERSON: Sure.

DR. NAIDU: This is a very challenging question. We have three devices that we have to be concerned about. One is nuclear replacement devices, the other one is the spacers, and lastly we have to address the pedicle screw system.

The spacers, the interspinous ligament spacers are supposed to be less invasive like the Back Stop devices, the Wallis device. They work on the premises that there is going to be distraction across

the space so the theme here is that it is less invasive. It can be done with local anesthesia.

How about the nuclear devices? They come in two flavors. Apparently they are injectable at times. At times they will need open surgical approaches. It also comes in many flavors. Costarica himself said the nuclear devices may have to withstand as much as 100 million cycles of load over 40 years.

They come in many flavors. It could be polyurethane. It could be elastin silk polymers, copolymers. They come in hydrogels, polycarbonite urethane, plastic polymers that are injectable to polymerize at 66 degrees celsius. Even though there is no actual curing occurring it is injected.

That is, molded into the disc space which is technique dependent because the surgeons don't have a mold of the space so instead of cutting a metal mold, the spine itself is actually serving as a mold. They may not be benign devices even though it appears that unless we inject this material, it may be benign. It may not do anything.

I don't think these things have been

characterized adequately in the literature as well. There are reports as far as oxygen degradation reports. I think polymer characterization is an important issue here. That goes back to preclinical issues.

Now, coming back to the appropriate time to intervene, it is the general consensus of the panel that the patient population is quite varied. Some numbers that come up for a young patient with acute disc herniation six months may be too long a time.

Early intervention may be appropriate. I do agree with that. People with spinal stenosis a more definitive time of six months as FDA has already required it would be more appropriate. Those are my thoughts. Have we addressed the first question adequately?

MR. MELKERSON: Let me possibly redirect it a little bit. What we are looking at here is suggestions on inclusion/exclusion criteria. We are talking homogeneity of the group devices. If a sponsor wants to study a particular device and they want to pursue a particular group, you have talked

about herniated disc acute. You have talked about degenerative processes.

Suggestions in terms of giving not only FDA but the industry guidance of instead of trying to have a very heterogenous population, would the suggestion then be from the panel then to try to limit your studies to stenosis, herniated disc acute.

In other words, when we're looking at this question, it is trying to address how do we advise and work with sponsors to identify inclusion/exclusion criteria for them to study to get to a point where you then can compare it to a control group.

The time to intervene question is looking at when we are trying to help people design studies, where are we going with inclusion/exclusion criteria to be appropriate candidates. There is a suggestion then to keep it -- have them limit their groups based on, say, acute herniation or degenerative processes. I would kind of turn it back to the panel.

That is where the intent of this question was, not trying to lock you down and say, "We need X, Y, and Z for each study design." What are the points

to consider in giving advice to companies that are. In other words, it may be premature to initiate guidance at this time but the studies, and we are being approached with those studies at this time, what advice then would you have in that vein.

DR. NAIDU: Dr. Yaszemski.

DR. YASZEMSKI: I think it would be appropriate to match both the disease and the device in each study and start with that. For example, a posterior motion limiting device to the neutral zone for back pain associated with degenerative disc disease and start that with a description and have the inclusion and exclusion criteria flow from there.

So I think that even saying that, I still can't find myself giving you a number because I think that number is going to depend on what that device is, what the intended target audience is, and what the inclusion/exclusion criteria are.

At the point of seeing that for each application, I think then clinical and scientific criteria could be applied to that combination of disease patient group and device to come up with an

appropriate number. I think that number is going to vary widely for the different combinations of diseases and devices that we've talked about today.

DR. NAIDU: Dr. Rudicel, anything to add?

DR. RUDICEL: I think age criteria obviously as well. Otherwise, nothing else.

DR. NAIDU: Dr. Kim.

DR. KIM: I would agree as well. It is worthwhile from a scientific basis to try to get as clean a data as possible so that we can make a solid conclusion as to the results. I would recommend that we focus on each disease entity assuming that the device being studied is appropriate for that entity and that is what it's designed for.

Some devices are designed for two things so the question arises if one device treats two different things, should we just include both those things in the same study. That depends but let's assume two extremes. One is stenosis and the other is herniated disc. I think we should have two separate inclusion criteria. If you are going to go through that trouble, it's probably cleaner to have two

separate studies. That's what I would vote for.

Also, I get a sense that this problem is so big that we are not wanting to try to come up with a number but I would encourage us to work with the study sponsors and investigators to come up with something so that there is not such a wide variability in the different studies that we are going to be evaluating at this panel. Just for selfish reasons I want to be able to come to a solid decision. It will be difficult if two very similar devices have two very different inclusion criteria.

DR. NAIDU: Thank you, Dr. Kim.

Dr. Diaz.

DR. DIAZ: I think the answer to your question is one word, specificity. You have to look at what problem you are trying to resolve and apply the possible tool to solve it. Once you have identified those two things, then your inclusion criteria are narrow. The broader the inclusion criteria, the bigger the population that is required and the less likely that you will get a good answer.

I think if we can narrow the question to

one problem, one device, one application, then you can come up with a very well tailored-down solution to the problem and it will give you a better yes or no answer rather than making it fishnet.

DR. NAIDU: Thank you, Dr. Diaz.

Ms. Whittington.

MS. WHITTINGTON: I agree with the panel. I have nothing further to add.

DR. NAIDU: Ms. Adams.

MS. ADAMS: I have only one other thought to add, is that Dr. Mathews talked about smaller studies, shorter-term endpoints. I like the idea of specificity and I think maybe we may be moving towards a place where we are talking about companies working with clinicians to look at some specific state. We should also be considering looking at a variety of studies that are smaller and have shorter endpoints so that we can get more data.

DR. NAIDU: Thank you, Ms. Adams.

Mr. Melkerson, in general with regards to Question 1, again, the time criteria is quite varied. The specific recommendation will go to the fact that

the disease process be matched to the device. For example, if somebody has stenosis, go with the distraction device. If somebody has a disc issue, go with the nuclear replacement device. That way we can narrow the patient population down and develop more stringent criteria. Does that adequately address it?

MR. MELKERSON: I believe so. Thank you.

DR. NAIDU: Thank you. Let's proceed on with Question No. 2. Would you mind reading it, please? Thank you.

MR. PECK: Based on the population of appropriate surgical candidates discussed in Question No. 1, please discuss the control options, nonoperative or operative, for each of these device type. Please consider that a clinical study must be designed to demonstrate a treatment effect.

For example, it must be designed to show that any observed clinical outcome is due to the device rather than other confounding factors and treatments. When considering this issue, please consider the following dilemma. On one hand, in order to warrant surgical intervention patients may have

results to nonoperative therapy options.

However, on the other hand, a patient should not be randomized to a control treatment that they have already "failed."

Also, remember that these patients may not meet the currently used criteria for surgical intervention. Please comment on the use of "crossover" and secondary treatment designs. Specifically, please comment on how to define patients who have "failed" the first treatment and thus are eligible to go on to the second treatment.

DR. NAIDU: Thank you. Dr. Kim, would you like to lead off, please?

DR. KIM: The question is to whether or not we need controls. The answer is an overwhelming yes. The question is what type of controls. I think that's what we're talking about. Probably the biggest concern that most sponsors have is do these controls need to be randomized.

I think the answer to that is clearly no. We can use historical data. We can use crossover data. We can use a number of different things. We

need to be flexible but we need to be stringent in our analysis and in the end that is going to require reliable data.

So when we sit down and decide on a study whether or not the control is adequate, it always depends on the disease entity to be treated and what is the current accepted treatment. Sometimes the answer to that is not obvious as we can see. I don't think, at least myself as a panel member, will be able to sit down today and tell you what the answers are.

In the end I think we need to spend more time and we need to be more focused not on a case-by-case basis but on a disease entity and type of implant basis. In some cases we should consider having three groups. If we are in a situation where you have a device to be studied and the two potential controls are either nonoperative treatment or fusion, for example, even that may be an appropriate type of study.

I'm sorry to say I can't give a specific recommendation but I do want to emphasis that the FDA needs to be flexible and, again, work with the study

sponsors and investigators to come up with an acceptable study design.

DR. NAIDU: Thank you, Dr. Kim.

Dr. Diaz.

DR. DIAZ: I guess in this situation I'm going to be the bad apple. I believe that the only way we can come up with an answer is if we compare apples to apples. I think a study design of this nature requires the assessment of the best possible treatment versus a new option.

If the only available best overall treatment now for this disease process or any of these processes is nonoperative, that has to be the control because we don't know that there is anything better yet. If we are looking for a scientific answer, we have to compare what we have now with what we are proposing. In my mind the control has to be always nonoperative versus operative.

I disagree completely that a historical control is adequate. In my mind if we want to come up with a scientific answer, we have to have concurrent controls. Otherwise, we will not answer the question

and we will leave it open for somebody else to criticize us.

I think we have to have concurrent controls that are randomized as best as randomization can be done. I have seen far too many studies that have been approved and then shot down scientifically because they lack concurrent randomized controls.

The randomization into the study in my mind should be done probably relatively early. We are not really in a position right now to tell how long a nonoperative treatment is. Since what we are trying to answer is whether nonoperative is better or as good or not as good as surgery, then I think on early entry into the study is acceptable because that is a question we will answer with this study.

If we choose six weeks, three months, two days, I don't think it's quite as important as including that nonoperative branch as a very important point of comparison with the operative component.

Once we have come up with that answer, we will know that if our nonoperative group got better at three months or six months, then we will be able to

say when the study population that was operated on and got a better result we can say these people will improve with medical therapy or nonoperative therapy if they do so within six months. If they don't, then surgery should be indicated. I think that time limit is more applicable to the future implementation of the device used.

I am in total disagreement with crossover allowance. In my mind a crossover allowance is not scientific. To me somebody that fails treatment can and should be treated outside the study but should be considered a study failure, not entered into the study branch on the other side of the population. If there is crossover treatment, they should be given the treatment but taken out of the study.

DR. NAIDU: Thank you, Dr. Dias.

Dr. Rudicel.

DR. RUDICEL: I think theoretically what you're saying is right and is the most ideal way to get a really pure answer. I think in reality that sometimes doesn't work which is why I was making the point of thinking outside the box. And it may even be

things like starting people early in a trial and there may be a second point beyond that at which randomization might occur as well.

I also agree with you about the crossovers. I think they are treatment failures even though they deserve to have the treatment offered. It's complex and I still believe concurrent controls are certainly the best but I think we do have some good current historical controls so I think there is a place for that as well.

DR. NAIDU: Thank you, Dr. Rudicel.

Dr. Yaszemski.

DR. YASZEMSKI: Receive from this discussion not the issues of time to treatment and control groups are interrelated. If the person who is the patient has reached what they consider the end of nonoperative care and the timing allowed by the inclusion criteria of the study aims at that time, whatever that time be, then they are not going to be at a point where they are going to want to be randomized to a nonoperative arm which brings up why there is an issue of operative versus nonoperative

controls.

I think that I am going to agree with Dr. Diaz that to have a valid assessment of whether early intervention is appropriate, it needs a nonoperative control but that also implies that the time at which you make that decision has to be sooner so as we got to that spectrum we've been looking at, six weeks to six months, if we are going to have nonoperative controls, then we would have to have the ability to offer to persons earlier in the course of treatment and not at a point where they've had enough and are looking for a different kind of treatment and will not accept a nonoperative control.

I think that will eliminate the issue of the crossover because people when entered into early are still at a point where they are thinking, "Well, is there equipoise? Is it equally beneficial to me to either continue to try nonoperative therapies or to try one of these early interventions." If you allow the studies to enroll patients at that point in their care, then I think the issue of crossover will go away. I would agree with allowing an earlier time

point if and when a nonoperative control arm is approved.

DR. NAIDU: Thank you, Dr. Yaszemski.

Ms. Whittington.

MS. WHITTINGTON: I agree with Dr. Yaszemski. I think certainly what we're hearing today offers or provides patients earlier treatment than we have historically had for back pain and that's a whole different ball of wax for everyone to deal with.

Earlier treatment will allow people to select operative treatment earlier. I agree that there should not be a rescue procedure included in the results. They should be a failed treatment. Otherwise, we have no good comparison.

I think we have seen in other studies that having a good control group is the one thing that we depend on to help us -- one of the things that we depend on to help us in making decisions as to the applicability of the study summary to other patient populations.

DR. NAIDU: Thank you, Ms. Whittington.

Ms. Adams.

MS. ADAMS: Well, I think I agree with Dr. Rudicel in her comment to Dr. Diaz in that I understand the pure approach he's interested in. I think there is real practical considerations here. One of the things we talked about yesterday that strikes me is that we have different -- we have a referral system and so we are talking about, as I understand it, primary care physicians and specialist.

Where do we talk about when a patient is entering this whole continuum of care and at what point they think they failed or that sort of thing. That's one concern. The other is that I thought Dr. Anderson's point was very good in that if you are thinking about control groups, these patients have very different opinions and personal strategies regarding what they do and don't want to undergo.

How we dial that all in is also a complicating factor, I think. I don't have a particular answer but I do have concerns along those ways and I'll leave it at that.

DR. NAIDU: Ms. Adams, thank you.

I would have to concur with Dr. Diaz. I

think an ideal study would require a nonoperative control group. He has said little concern about the crossover and I do have to concur with that as well. I don't think crossover should be allowed. I think they should be treated as treatment failures.

Lastly, Dr. Yaszemski points out clearly that if you do limit the nonoperative time, rather than prolonging it to six months, maybe even shorter, the issue of crossover may go away. In general the panel believes that randomized nonoperative controls would be a reasonable control group and, in fact, is a needed control group to judge the efficacy of the device that is being implanted.

Have we addressed that question adequately?

MR. MELKERSON: Actually, my staff has given me a couple of questions but I want to ask one of my own questions first. We have been talking about nonoperative controls or surgical controls in terms of study designs.

Now, in discussions if they are ready for surgery, are there for these devices -- we're talking

about devices. Are there surgical treatments that could be considered to be used as controls of these minimally invasive earlier intervening devices and how would that figure into your discussions in terms of a control group?

DR. NAIDU: Dr. Diaz, would you like to address that?

DR. DIAZ: Yes. In my mind we are trying to open a new chapter in the management of spine disease. We are trying to look at something that has not been really treated commonly surgically. Again, I have to be a purist in that regard.

I don't think there is any surgically comparable group that exists currently, at least in the U.S., that has been approved or accepted by standard of care as appropriate for the care of these limited or intermediate back pain patients.

So, in my mind, no, I would not accept the surgical comparison because we don't know that there is a surgically acceptable treatment yet. In my mind it should be nonoperative and operative for each one of these devices.

DR. NAIDU: Thank you, Dr. Diaz.

Dr. Yaszemski.

DR. YASZEMSKI: Nothing to add.

DR. NAIDU: Dr. Rudicel.

DR. RUDICEL: Nothing to add.

DR. NAIDU: Dr. Kim.

DR. KIM: Dr. Diaz' comments are all excellent but I would personally not want to pigeonhole the investigators to that type of requirement in case a particular study and device has an operative control.

The one that I can think of is using a nucleus replacement device to fill the void that you would after a discectomy that control so the disease would be herniated disc, the device would be the disc replacement device to try to prevent, for example, long-term back pain or progression of degeneration.

In that case, to make the control group with leg pain or radiculopathy be a nonoperative control, I don't think that would be very beneficial so most of the time it will be nonoperative treatment, particularly if the sponsors and investigators claim

that this treatment is for a group of patients that are bad enough to be suffering but not bad enough to warrant surgery. Then the appropriate control is nonoperative but there are going to be instances where that is not the case so my vote is not to pigeonhole it at this point as of yet.

DR. NAIDU: Thank you, Dr. Kim.

Ms. Whittington.

MS. WHITTINGTON: I have nothing to add.

DR. NAIDU: Ms. Adams.

MS. ADAMS: Just one thought and that is that we have heard things about smaller studies, earlier time points. We have also heard things about randomized controls, nonoperative controls, and specificity. All of these things are at play. I'm a little bit concerned that if we give advice back from t his panel that says we need to be specific, we need to be randomized, we need to have controls. We are talking about long lead times for most of these devices and these are things that we need to dial in.

DR. NAIDU: Thank you, Ms. Adams.

Mr. Melkerson, you've heard varied

responses -- yes, go ahead.

MR. MELKERSON: Could Mr. Stiegman actually ask his question? I'm having difficulty reading his writing.

MR. STIEGMAN: Glen Stiegman, Branch Chief, OPA Devices Branch. One of the issues that we keep coming up with when trying to figure out a control for this is we go through the continuum and look at how the device is indicated. We agree that these devices can't be generalized across the board and they are looking for specific answers.

However, when looking at those early option devices maybe for acute rugby player, and not good looking rugby players but acute disease rugby players, is it really ethical to implant this device? You are going through a surgery, the risk of surgery.

I think Dr. Yaszemski hinted at it, weighing the risk and benefit of the two control and investigational arm. If there is an option or a chance that this patient may get better through conservative care, should they be randomized to get a surgery?

DR. NAIDU: Would anybody like to address that? Dr. Yaszemski.

DR. YASZEMSKI: I would say that's the person's decision. If the patient meets the inclusion criteria, it doesn't mean you are going to randomize them. It means you offer it to them and if they feel they are still at a point where they may get better, they will choose not to participate in the study.

I would say as long as from clinical view we feel there is equipoise in the treatments from a scientific view, the data that emanates from the study will be valid, then presented to the patients and they will decide whether to sign up or not.

DR. NAIDU: Thank you, Dr. Yaszemski.

Dr. Rudicel.

DR. RUDICEL: Yeah. I would completely agree. I mean, I think we wouldn't have any innovation at all if we said it was never ethical to offer patients options. That is really part of the ongoing studies. We do as much as we can beforehand to approve safety and efficacy and then offering patients that option is what is going to lead us to

find new treatment modalities that will be beneficial.

DR. NAIDU: Thank you.

Dr. Kim.

DR. KIM: I agree with both Dr. Yaszemski and Dr. Rudicel.

DR. NAIDU: Dr. Diaz.

DR. DIAZ: I think the purpose of the FDA, as I have understood it in the last five years of participating in these panels, is to look at two questions: is the device safe and is it effective? If the questions that we have to answer are premised on those two concepts, then doing a scientific study that answers those questions is a must.

That is why we have to in my mind be relatively strict in including individuals that are limited in scope of need and particular in a type of problem for a specific device. We offer it to the patient. We say, "This is the potential benefits to you and these are the potential risks. It is up to you to help us decide if this is the right treatment for people like you. We don't know that this works any better than aspirin. Do you want to participate

or do you not?"

DR. NAIDU: Thank you, Dr. Diaz.

Ms. Whittington.

MS. WHITTINGTON: As the consumer representative on the panel, I really emphasize the fact that we cannot take patient choice out of the potential for an invasive procedure. To do that would not be appropriate in any way.

DR. NAIDU: Thank you, Ms. Whittington.

Ms. Adams.

MS. ADAMS: No comments.

DR. NAIDU: Did we answer your question?

MR. STIEGMAN: Yes. Thank you. My second chicken scratch comment was -- I mean, like I said before, you can't really generalize these devices. However, we have discussed acute devices that there is an immediate need for and then those like stenosis that may be more long-term where six-month entry criteria is needed.

I still really haven't heard and maybe this answer doesn't exist yet but what would be the control for at least those two groups of patients? I

mean, if it's acute, should we have the conservative care? I mean, I would like to hear the panel actually say that. If it's an acute type indication, should conservative care be used.

Or if it's long-term and it's minimally invasive surgery and six-month conservative care entry criteria, should bigger surgery such as either disc replacement or fusion be used. Basically two different categories of indications.

DR. RUDICEL: Could you clarify that again? You want to know if there should be conservative care?

MR. STIEGMAN: I guess from what I've heard from discussion from Question 1, I heard two sort of devices discussed, one for acute care and one for more long-term where six-month inclusion criteria will be needed or conservative care criteria will be needed.

What would you suggest or what would be your input on control for those two types of scenarios? I don't know if I specifically heard that discussion or, at least, not to my satisfaction.

DR. NAIDU: Dr. Yaszemski.

DR. YASZEMSKI: I'll take one of them. I'll choose what you have referred to as the long care one and, if I might, I'll rephrase that. I wouldn't call it long-term care. I would call it treatment for a disease that develops slowly and steadily, i.e., the stenosis patient as I think you are getting at.

I think that you have come to an example now of the general to the specific. You have asked for a specific mix of patient, their position along the disease spectrum, their symptoms, the chronic symptoms, if you will, the spinal stenosis and claudication, and a type of device. In t his case I would think you would be talking about perhaps the interspinous devices that will flex the functional spinal unit.

I would say that this would be an example of this particular mix. I think that this is the way it's going -- from my perspective this is the way it's going to have to be addressed. What we can do here is a frame work to which we can apply to specific mixes of patient device and proposed treatment.

I would say that this type, a person who comes in with spinal stenosis, I would shorten the time to which I would offer that person entry into a study for an interspinous process device because these persons typically have comorbidities. They have heart disease. They have lung disease. To offer them something that can be done under local anesthesia I think is a big plus for them.

In my practice if I saw a study available that would allow me at the time I went from activity modification, anti-inflamatories, physical therapy for a stenosis patient to injections for a stenosis patient, I would think there would be equipoise of treatment to offer that person entry into a study that would allow them an interspinous device.

I think the risks to them would be low enough.

That is just one guy's opinion and I think this mix of all these factors is going to occur with everyone of these proposals like you just said. So I would shorten the time for this particular patient and include it with nonoperative treatments such as

injections.

DR. NAIDU: Thank you, Dr. Yaszemski.

Dr. Rudicel.

DR. RUDICEL: I just wanted to add to that that a person like that also may be coming to the physician when they are well into the course of their disease. It may be that there are some instruments, maybe the SF-36 or some type of instruments that can give a bit of an indication of just how much their symptoms are affecting their life which is the most important thing.

But I would agree they need to come to treatment much sooner than the football player that herniates a disc acutely so that, you know, it would be good if there is a way of measuring at what point in their disease process they are entering the medical system. I think that affects the entrance into the study and treatment.

DR. NAIDU: Thank you, Dr. Rudicel.

Dr. Kim.

DR. KIM: I would agree with those comments.

DR. NAIDU: Dr. Diaz.

DR. DIAZ: I just noticed a little fragment of your comments that bothered me a little bit. The issue that I picked on was that if this patient has been treated conservatively for six, eight, 10, 12 weeks, is that an acceptable control to that patient already and should that patient be then treated surgically and can we use the person as his own or her own historical control?

In my mind that is not acceptable because the way that I treat back pain, which may include a six-pack per night, hot packs locally, and resting on the beach may not be the same as Dr. Yaszemski who treats them with nonsteroidal anti-inflammatories, physical therapy, ultrasound, and epidural injections.

So a rose is not a rose is not a rose here. Conservative treatment does not mean the same thing to all of us. It is a very different thing. It is not the same for a primary care as it is for a spine specialist. We need to make -- if we are going to answer the question, we have to answer the question directly.

Is it appropriate? The operative word here is appropriate. Is appropriate conservative therapy better, worse, or equal to operative treatment? If that is the question we want to answer, then all of these patients should be treated equally. They should be entered early into the study and they should be given the same management.

If nonoperative treatment is good, we'll know it then but it will be the appropriate nonoperative treatment. To me of all the four questions you gave us, this is the easiest one to answer because it applies to everybody. In my mind there is a very simple answer to this. It is nonoperative versus operative specifically driven to each individual population.

DR. NAIDU: Thank you, Dr. Diaz.

Ms. Whittington.

MS. WHITTINGTON: I think Dr. Diaz brings up a good point. What he's talking about is evidence-based practice and evidence-based guidelines. That is an issue across the board, not only with this disease but other diseases and practitioners, orthopedic

surgeons, neurosurgeons, and primary care physicians need to be providing care at the same level.

Until we can get to that point, I'm afraid that Dr. Diaz is right, that patients that are included in these studies have to undergo what those guidelines are from the point that they are entered in the study. If prospectively that changes and people truly are using the same guidelines in conservative management of these patients early in their disease, then that could potentially change but that is not in the playing field right now I don't believe.

DR. NAIDU: Dr. Kim, you had something to add?

DR. KIM: I'm sorry. We're going out of turn but I just want to bring up a point. All those points are very valid scientifically but the reality is that there are going to be instances when a new device is very, very promising and whether we like it or not, these devices are already being used outside the U.S.

If as a panel member I was presented with data from outside the United States that had valid

outcome measures, was well controlled whether randomized or not, and the disease entity had a good historical control, for example, lumbar stenosis, the results of that are very well known historically, then I would feel uncomfortable making that device undergo a stringent randomized control trial that would take four or five years when we have enough data to reasonably say that this is safe and it is effective based on the data that we have at hand.

Most of here are M.D., Ph.Ds so I think we are all scientists but at the same time we are also clinicians and I just want to reemphasize that, at least, from this seat that being stringent and scientific is not necessarily what the goal of the FDA necessarily needs to be, at least from my perspective.

DR. NAIDU: Thank you.

Ms. Whittington.

MS. WHITTINGTON: I think that is a good point. Certainly spinal stenosis has radiographic indications that may be different than a disc herniation early on. Maybe that needs to be addressed in the application criteria or identification for

patients. Good point. Thank you.

DR. NAIDU: Ms. Adams.

MS. ADAMS: Well, I like Dr. Kim's idea. I think it's a creative approach and I think it is something that should be considered. I think one of the biggest concerns I have through this whole discussion is that we're talking about people who have probably failed conservative care and how do you dial them in and put them into a control group.

I think that's a real challenge so I like your idea. I can certainly imagine that somebody would say, "I would really be interested in one of these earlier intervention devices as opposed to jumping to surgery. I think that is a great suggestion.

DR. NAIDU: Thank you, Ms. Adams.

Dr. Diaz.

DR. DIAZ: I think we need to be very careful with straying too far from the straight and narrow. One of the major problems we deal with right now in healthcare in the U.S. is reimbursement. The FDA recently approved the use of Charité device. Now

we have had a great deal of problem betting reimbursement by a variety of reimbursing agencies claiming that the study used was inappropriate, not well controlled, and not scientifically based.

Patients may not be reimbursed for a procedure that helps them because a movement exist now to indicate that the studies that the FDA found to be appropriate satisfactory and sufficient to answer both questions of safety and efficacy may be actually trumped by people who do not think that they were appropriately done.

If we allow too many of these less scientific approaches in the use of these things, even though industry wants us to get this out to the public quickly, we may end up not being able to use it because we did not do the appropriate relatively rigid studies that we need to do to answer those critics out there who will prevent us from using them later.

Even though there are studies outside the U.S. that may suggest that these devices are useful, if we set up our study criteria as such that there can be people who have failed their branch of treatment

and can be taken out of that treatment and treated as a failure but given the option of surgical treatment, we are serving our population well.

We have answered that conservative therapy is inadequate and we have provided the patient with the care that he or she needs. The U.S. population demands that we do this right. I don't think that being rigid is inappropriate in something like this.

DR. NAIDU: Thank you, Dr. Diaz.

Dr. Rudicel.

DR. RUDICEL: I just want to make a comment that I disagree a little with what Dr. Diaz is saying and I completely agree with Dr. Kim in terms of having some other options. I would not judge what the payers of medical care, what kind of judgment they are going to make about safety and efficacy because I think what they are looking to answer is very different from what we are looking to answer so I wouldn't use that as a judgment for whether a device is good or not good.

DR. NAIDU: Thank you, Dr. Rudicel.

Dr. Yaszemski.

DR. YASZEMSKI: I'm going to submit that we're all saying the same thing. I think that the issue of U.S. versus non-U.S. studies should be based on whether there is good evidence-based medicine regardless of where the study comes from. If the study is from outside the United States and after scrutiny it appears that it's a good study, then it's appropriate to use that data.

DR. NAIDU: Thank you.

Mr. Melkerson.

MR. MELKERSON: One last point of clarification. This is to Dr. Diaz. I have heard enrolling patients in conservative treatment. Some of the study designs have already failed appropriate conservative treatment and then compared one of these interventions. Are you making a distinction between those two groups? In other words, should the studies be enrolling at the same time or is there a distinction in your mind?

DR. DIAZ: In my mind there is really no distinction. In my mind appropriate care needs to be defined beforehand. Once we know what the

nonoperative appropriate treatment is and we implement that, the comparison of nonoperative with operative is relatively easy and uniform. I cannot accept what somebody else has given us as appropriate nonoperative control and include that as my criteria because it may not be the same. It may be a lot better but it could also be a lot worse.

DR. NAIDU: Okay. Ms. Adams, did you have anything to add?

MS. ADAMS: Well, I would just like to go back and echo what Dr. Rudicel said. I am very concerned about us comparing the bar for reimbursement in SEMUS with what Congress has advocated FDA to do with respect to safety and efficacy studies. They are very, very different. It may well be that we'll see SEMUS get the same kind of congressional advocacy pushing them in a different direction than they are. I think we should be careful of not talking about reimbursement as part of this panel consideration.

DR. NAIDU: Thank you, Ms. Adams.

MR. MELKERSON: I think you've addressed our question on controls. Thanks.

DR. NAIDU: Would you mind posing Question No. 3?

M R . P E C K :

Please discuss the most appropriate clinically significant endpoints to evaluate subjects with mild to moderate lumbar degenerative disease. Please discuss what value, if any, there is in demonstrating a faster response as opposed to comparing responses at the final study evaluation time point, which has traditionally been 24 months for spinal studies.

If demonstrating a faster response is considered important, please discuss the length of time the response should last to consider the device a success. Please also discuss the value of potential mechanism of action endpoints. Which of the proposed endpoints might the sponsor be able to demonstrate and how.

For example, should restoration of disc height and disc hydration be shown through objective radiographic criteria? Finally, please discuss the endpoints for demonstrating if earlier intervention is

warranted because it alters or delays the course of the disease.

DR. NAIDU: Thank you. I would like to ask Dr. Kim to start off, please.

DR. KIM: Thank you. Let me try to address this in two questions. The first question is study endpoints. Do we need to wait 24 months for every single study. I think Dr. McAfee made a compelling argument that in certain circumstances you don't have to wait 24 months. We can get a lot of data at six months which will be reliably the same at 24 months.

I think the number 24 months should not be strict. It should be variable depending on the disease entity and the device treated. Having said that, we also never answer the question of long-term efficacy. That came up dramatically at the Charité panel meeting where this is a motion sparing device.

It's going to be loaded constantly so what happens at 10 to 20 years or even 30 years, that is an important very relevant question. the question is how should we deal with that. I don't think it's fair to

expect the sponsors and the investigators to do 10 to 20-year studies.

In terms of study time points we can go shorter but, at the same time, I think we need a more robust mechanism to look at things long-term. Right now we are using the post-market surveillance and I would recommend that we change that term from surveillance to post-market studies and be a little bit more strict on that end to try to address those two very different questions. That is for the study time points.

In terms of the outcomes, there are numerous outcomes but the few things that I notice is that it is hard for a panel like myself to determine whether or not a study is efficacious if multiple different study parameters or outcomes measures are being used. Even though they may be imperfect, I would encourage the FDA and the sponsors to agree upon certain types of or certain specific outcome parameters so that we feel comfortable making some sound data analysis decisions.

Then, finally, the question of mechanism

of action, the rate at which this device improves patient outcomes. I think that should be specific. If the sponsor investigator claims that this device will (a) help patients within six weeks whereas the alternative treatment takes six months, then that should be a study parameter we look at and use that as a gauge of whether or not this is successful.

The same thing with mechanism of action. If they claim that this prevents future disc degeneration or allows the disc to rehydrate, that should be a study success criteria. That is how I would deal with those issues.

DR. NAIDU: Dr. Diaz.

DR. DIAZ: I think Question 1 and Question 3 are basically similar in nature. They are too broad to really give you a specific answer. I think that each individual pathology state that we are addressing needs to have its own endpoint follow-up criteria and success measures in relation to the device that is being used.

If we are looking at a resolution of spinal stenosis symptomatology in an elderly

individual and we are addressing it with an interspinous blocking device, then we may have an answer within six weeks.

If we are talking about a dynamic stabilization with any of the various dynamic instruments that have been presented, the answer may not be as easy to obtain in six weeks and may require six months because the intervention is much more invasive. I think it needs to be tailored to the disease process and to the tool use.

DR. NAIDU: Thank you, Dr. Diaz.

Dr. Yaszemski.

DR. YASZEMSKI: Thanks. I'll start by commenting on the process. We now understand a little bit it's one process, early degenerative disc disease. The part of the question that says, "An assessment might be to halt the progression of the degenerative process," highlights a difficulty here. It's not going to get halted.

The point is that it's going to go on so success, I think, needs to include an appreciation that the process is going to continue. Hence, I think

it would tend to make we feel this question about earlier time points is important. If the person is uncomfortable with their current symptoms because the care hasn't worked, I think it would be reasonable to look at whether the time change of how long it takes them to get better has occurred.

It is a difficult question to distill down to a few words. I do think earlier time points are important. I think that what you are going to look at is going to be different for all of them. For example, in this case we're using the interspinous process spacer for early DDD as opposed to another use for it in the spinal stenosis patient.

For early DDD this would be -- the interspinous process spacer would be something that is not going to preclude further surgery, minimally alters the anatomy, can be taken out quite easily if its affect stops and it will affect neither the facet joints, which will get typical degenerative changes or the intervertebral disc.

On the other hand, a nucleus replacement is going to affect the intervertebral disc. It's not

going to affect the facet joints other than their motion. The pedicle screw base systems will affect the facet joints in that likely some insult to their anatomy, some insult to their capsule in putting the pedicle screw base system, is going to occur and whether that has a longer term affect on the degenerative changes in the facet joints, we're not going to know that over a short period of time.

On the other hand, if that pedicle screw base system limits motion to the neutral zone, it may have a beneficial affect both on the facet degenerative process and the disc. It's a long-winded answer to say that a quick -- to answer this question, Mark, I think is very difficult. I think that we have to be intentionally vague and you have to look at each of these submissions individually.

DR. NAIDU: Thank you, Dr. Yaszemski.

Dr. Rudicel.

DR. RUDICEL: What I would add is that I think looking at patient-oriented outcomes is clearly important. We spent a long time in the academy in the '90s looking at establishing validated instruments

that everyone could use so that your comments would be answered where we are always using similar outcome measures.

It's difficult but there are instruments. Which of those we need to use I'm not sure of in the spine but I think you would want to work closely with NASS because they have done a lot of work in this area. Getting standardized approaches is what is essential.

I would maintain that radiographs are of some importance but certainly way down the ladder what we really care about is how patients are functioning, what their pain level is, and what they are able to do. Clearly there are floor and ceiling effects depending on the age groups. The 20-year-old is much different than the 70-year-old but I think standardization and patient oriented outcomes are of most importance.

DR. NAIDU: Thank you, Dr. Rudicel.

Ms. Whittington.

MS. WHITTINGTON: I would echo what Dr. Rudicel just said. Certainly the patient reported

outcomes are the most crucial. In looking at those I would agree that the emphasis of utilizing the same validated tools across all studies would be helpful in specific devices.

More importantly looking not at the specific numbers that people score on those but the percent change is the area of most importance, that improvement as perceived by the patient. Also, Dr. Yaszemski's comments about the importance of looking at applying these tools at a much earlier time because we are looking at a mild to moderate disease and not a severe disease what is what we have historically been looking at is also crucial.

In determining those time variations again across studies or time increments would be really important so that we are comparing apples to apples. There certainly is also the need for radiographic and neurological assessment on the part of the physician as well but I would again lend emphasis to the patient reported outcome.

DR. NAIDU: Thank you, Ms. Whittington.

Ms. Adams.

DR. RUDICEL: Could I just add one thing? I'm sorry. I think it's also being shown generally in orthopedics that simpler instruments are working better than the longer complex ones. I think one of my suggestions to industry would be not to try to reinvent the wheel and develop your new instrument for whatever new device you are developing but rather looking at NASS or what has already been done because a new instrument just, you know, clouds the issue.

DR. NAIDU: Thank you, Ms. Rudicel.

Ms. Adams.

MS. ADAMS: Thanks for that comment, Dr. Rudicel. I agree with you. I think we all want the same thing. We want instruments that are validated so I think it's a great point. There is some good work that has been done in those areas.

The only things I would add to this is that I think we ought to consider, even though they're not here and we haven't discussed them, valid surrogate endpoints, looking at Baysian statistics to predict longer-term outcomes with shorter-term measures. All those kinds of things that we talked

about as options to try and get data earlier.

The last thing I would add is that the issue of evaluating the mechanism of action sure seems like a complicated one since in many cases we don't seem to even understand the source of the pain so that's a tricky one.

DR. NAIDU: Thank you, Ms. Adams.

Mr. Melkerson, in general with regards to Question No. 3 the panel's consensus is that in general for these devices we do not need 24 months of follow-up like we have for total disc replacement and spinal fusion devices. However, these may be device dependent.

Six months may be adequate. Six weeks may be adequate. That has to be defined. It has to be device dependent. Therefore, in general the study endpoints will be shorter but, nevertheless, this does not preclude the fact that post-market surveillance the long-term outcome may well need to be appended to the stipulation that you would formulate.

Lastly, the mechanism of device should be specific to the device, although it appears that the

panel is kind of split on what you use for objective criteria with regards to that. Radiograph is important. It appears that if the device states that it distracts the interspinous space, it will show by CT scan.

There are some panel members who feel that should be shown. There are other panel members who say that you are better off with the patient outcome questionnaire rather than relying on the radiographic parameters. As far as progression of the disease, who knows. I mean, this will go on most likely, as Dr. Yaszemski has said. Is the device going to stop it? Mostly likely no. Have we adequately answered all the questions?

MR. MELKERSON: Just a clarification on the issue of earlier time points. You identified and earlier time point may be appropriate and we're talking about premarket/post-market balance. Should there be some demonstration of maintenance of that correction or improvement as part of a premarket requirement versus a post-market requirement. You had suggested maybe six months and I think Dr. McAfee had

identified maybe a year.

That would be a question that I would turn back to the panel in terms of when you're talking about earlier time points should there be at least some duration of effect shown premarket prior to putting other things off for longer term. That is, how long is the duration of effect last.

DR. NAIDU: Dr. Kim, would you like to address that?

MR. MELKERSON: And just a little caveat to that question. In terms of when you are looking at these earlier time points, what duration of effect before you would go on to another surgical procedure may enter into that mix.

I just kind of throw that out in your thought processes. In other words, if it's a duration of effect, what is appropriate for a patient. In other words, justify that this surgical intervention is as good as nonoperative care in terms of preventing going on to a more invasive surgical procedure.

DR. NAIDU: Dr. Kim, would you like to address that?

DR. KIM: That's a really difficult question. Yes, if that is an issue in terms of the analysis for the particular device and disease entity, then we should do longer-term premarket approval. The question is what number is it. I really like the analysis Dr. McAfee gave with the Charité that things seem to plateau at about six months.

I would want to look at data like that a little bit more to get a good idea of how solid that six-month or 12-month data is. Again, I like six months, I like 12 months. Twenty-four months is even better but it may be too burdensome. To answer your question, yes, we should look at premarket parameters to look at durability. The question is how long do we need to look at it. That is going to require a little bit more study that probably the data is out there.

Then how long should we wait. I think the answer to that is completely dependent on the answer to the first question. We just have to find out how durable an implant is within a reasonable degree of certainly.

DR. NAIDU: Dr. Yaszemski.

DR. YASZEMSKI: I think, Mark, my answer would depend upon what the risk to putting a particular device in was and what the alteration of normal anatomy was and how easy it is to remove the device.

On the one end of the spectrum if it's very low risk to insert under local anesthesia, disrupts normal anatomy very little and can be removed with minimal risk, I wouldn't ask for long-term results at all. I would say if it provided quick relief of the symptoms and lasted a short time, whatever you define as short, I would be okay with that.

I wouldn't ask for -- to put a number on it I wouldn't even ask for six months if it were easy to do and low risk. On the other hand, if it was risky to put in and risky to take out and altered the anatomy a lot, I would want to know that it's going to last longer. For longer I would make the one or two-year number.

DR. NAIDU: Thank you, Dr. Yaszemski.

Dr. Rudicel.

DR. RUDICEL: I would concur with that.

DR. NAIDU: Thank you.

Dr. Diaz.

DR. DIAZ: I think the only comment I have to make on that is really are we talking about early success response or are we talking about delayed sustained response. If it is early response that we are looking at, the device used and type may give you a very wide spectrum of responses.

The simple device that requires minimal implantation effort may give you a quicker answer to a very specific problem shortly. As opposed to the one that requires a lot of intervention with a lot of local tissue damage that requires time for healing in and of itself.

If we are talking about duration or length of duration of response, sustained response, then I think we are looking at a totally different thing because, as was mentioned earlier, this is not a static process. It is a dynamic process. Even though we may intervene surgically to try to slow it down, we are not stopping it.

So the durability of a procedure may be addressed again individually to the specific device with the understanding that the process in and of itself has a fairly steady rate of progression that we may alter to a certain point and we don't really know what the natural history of the problem is in addition to what the intervention will do to that natural process.

DR. NAIDU: Thank you, Dr. Diaz.

Ms. Whittington.

MS. WHITTINGTON: I have nothing to add.

DR. NAIDU: Ms. Adams.

MS. ADAMS: (No response.)

DR. NAIDU: Have we adequately answered that? It appears as if co-primary endpoints seem to be reasonable for some devices, whereas the other devices which are less invasive we may not need to stress the co-primary endpoints. In fact, we may not even need the one-year or two-year data for those.

MR. MELKERSON: Just a quick response to Dr. Diaz. Some of the questions are aimed at some of the claims sponsors want to make so I appreciate your

looking at early claims versus later claims because some of them have actually said we stopped degenerative process so the duration question comes into play.

The review staff has also asked part of this question was related to the types of evaluations done, ODI, ZZQ evaluations. I've already heard patient satisfaction. Are there other types of studies or should we just be going to the professional societies and looking at their mechanisms?

NASS identified one of their own. Any comments on those as far as adequacy for these types of devices? In general, if I'm not mistaken, many of them were looked at more for the more invasive type devices. The question is are they relatable to these devices?

DR. NAIDU: Thank you.

Dr. Yaszemski, would you like to start off on that?

DR. YASZEMSKI: Mark, I'm not sure I can give a straight answer to that. Again, my response is going to be that heterogeneity is going to require

considering a particular mix of device indication and risk. I'm going to stay vague and not directly answer.

DR. NAIDU: Thank you.

Dr. Rudicel.

DR. RUDICEL: I think that is a very good question and I'm not really qualified to answer that either. I would certainly look to -- I know several people in the spinal world I would look to to help answer that. I think that is probably what should be done.

DR. NAIDU: Thank you, Dr. Rudicel.

Dr. Kim.

DR. KIM: I agree. I don't think we can make a decision today but we should probably formulate a panel of experts to come to a decision at some point because there are instruments out there that are being used very frequently compared to other instruments and we should make a decision on that.

DR. NAIDU: Thank you, Dr. Kim.

Dr. Diaz.

DR. DIAZ: I think it needs to be process

and disease specific device tailored and with a recommendation from professional societies.

DR. NAIDU: Dr. Whittington.

MS. WHITTINGTON: Again, I think NASS is a good source of that but ensuring that there are validated tools, that there are some generic tools like an SF-36 that I think probably are too generic for this patient population quite frankly but I think utilizing those resources. Patient satisfaction is not the only thing to be evaluated here but patient pain and functionality are the two most crucial pieces to evaluate.

DR. NAIDU: Thank you, Ms. Whittington.

Ms. Adams.

MS. ADAMS: No comment.

DR. NAIDU: Have we adequately addressed that issue?

MR. MELKERSON: I think we've --

MR. PECK: One point of clarification maybe. On the mechanism of action point, it seems like the panel is saying you definitely agree if the sponsor makes a claim that should be validated in the

study.

However, if we get an application and it doesn't make any specific mechanism of action claims, our concern is that if we are comparing these patients to these earlier conservative care as a control, we are going to be left with patients that get better in the investigation but we're not going to be sure if it was due to just them getting -- the fact that they might have gotten better anyway if they continued with conservative care. That was one of our main concerns with mechanism of action.

DR. NAIDU: Thank you. Dr. Yaszemski.

DR. YASZEMSKI: Now I can offer a thought because that is a specific question. I think I'm going to get back to what Dr. Diaz said before. We'll answer that with an appropriate design study that has an appropriate control group. That is a straightforward question.

DR. NAIDU: Dr. Kim, anything to add?

DR. KIM: (No response.)

DR. NAIDU: Dr. Diaz?

DR. DIAZ: No.

DR. NAIDU: Anybody else?

MR. MELKERSON: I think you have adequately addressed this question. Thank you.

DR. NAIDU: Thank you. Would you mind posting Question No. 4, please.

MR. PECK: Please discuss what changes to traditional spinal device study designs might be appropriate given the less invasive nature of many of these devices as well as the mild to moderately affected patient population. Please discuss the appropriate final time point to evaluate study endpoints to make a determination of study success.

Please discuss whether it is appropriate to define a small change in pain and function scores as clinically significant given that these devices may pose less risk and that the inclusion criterion score may be lower and the ceiling effect may come into play.

Depending on the study control, please discuss noninferiority versus superiority. Also, please discuss whether an increased delta may be appropriate depending on the control.

DR. NAIDU: Thank you. I think that we have already answered some of these questions but I would like Dr. Diaz to field this question.

DR. DIAZ: I cannot answer it any better than in Question 3. I think the study duration, the appropriateness of response, the outcome superiority or inferiority needs to be tailored to the disease process and to the device used.

If we use appropriate criteria that have been selected with the help of the professional societies, that will answer not only the clinical improvement criteria that we need to know, but also the anatomical criteria that some of these devices claim to make a change to, then that has to be applied to each and every one of these problems and tailored accordingly.

DR. NAIDU: Thank you.

Dr. Kim.

DR. KIM: This is a very difficult question as well. Sitting here it is painfully obvious that we do not have enough information to say with any degree of reasonable certainty that we know

what numbers represent success.

The numbers that we have we have because we needed to have them to look at the past PMAs but I think it's an opportunity now to go to literature and try to better define and validate the degrees, the numbers that better represent what is successful and not successful in the study using the particular instruments that we are recommending be used.

The second question is whether or not a smaller change in pain and function is clinically significant. I think that speaks to the first question. If I was faced with a situation where -- that was brought up in one of the presentations, one treatment is much more dangerous. Yet, if it's successful, the outcome is greater than a much safer minimally invasive option but the overall success is slightly less, I would not be against that type of success criteria.

DR. NAIDU: Thank you, Dr. Kim.

Dr. Rudicel.

DR. RUDICEL: I don't really have much to add except that clearly I think we are going to have

to alter what is considered successful. I think definitely a different delta may be indicated.

DR. NAIDU: Thank you, Dr. Rudicel.

Dr. Yaszemski.

DR. YASZEMSKI: I think that in general if the treatment is less invasive, if it's earlier on, than I would tend toward liking this improvement of 10 points over the traditional 15 points. For example, the Oswestry. I would tend toward liking a larger delta value in return for earlier intervention with a more minimally invasive treatment. And add the caveat that not everything we are talking about here is minimally invasive. This would be for those that are minimally invasive.

DR. NAIDU: Thank you, Dr. Yaszemski.

Ms. Whittington.

MS. WHITTINGTON: I have nothing to add.

DR. NAIDU: Ms. Adams.

MS. ADAMS: Well, this may surprise you but I agree with Dr. Diaz that we should be basing these parameters on the device, the disease, and the study objectives. I think it's a great idea and

certainly well worth considering that with earlier intervention for lesser diseases. As Dr. Schneider said, smaller changes in outcome scores are inevitable and should be expected so I think it should be considered.

DR. NAIDU: Mr. Melkerson, to summarize the panel's thoughts on this, in general the panel believes that if the device is less invasive, smaller changes in pain level may be acceptable, higher delta values may be acceptable. Again, everything should be just based on a specific device and the mechanism of action. Again, not all the devices that we are talking about today are of the same mechanism. I mean, some are definitely less invasive than others so, again, they have to be again device specific.

Anything else that you would like us to address?

MR. MELKERSON: Just because we keep using the term minimally invasive and less invasive, just for clarification to make sure that we are understanding correctly, what you're calling less invasive are the stenosis type spacer products that

can be done under local? How would you grade the nucleus replacement products whether injectable or noninjectable and the pedicle screw base systems?

DR. NAIDU: Why don't we go around the table and try to get an opinion with regards to that.

Dr. Yaszemski.

DR. YASZEMSKI: If it's an injectable nucleus replacement first. If it's injectable and done at the time of a surgery that is already being done, I don't think there's any increase in risk. It's already an open surgical procedure. If it's an injectable percutaneous nucleus replacement, I would call that minimally invasive.

If it's an open surgically implanted nucleus replacement, I would consider that a standard surgical procedure and neither minimally nor less invasive. The pedicle screw systems, if they can be applied under sedation and local anesthesia percutaneously as some are, I would consider that less invasive.

If they require an open surgical procedure, I would consider that a normal surgical

procedure neither minimally nor less. Finally, the interspinous process spacers I would consider them minimally invasive.

DR. NAIDU: Thank you, Dr. Yaszemski.

Dr. Rudicel.

DR. RUDICEL: I don't have anything to add.

DR. NAIDU: Dr. Kim.

DR. KIM: I concur with Dr. Yaszemski.

DR. NAIDU: Dr. Diaz.

DR. DIAZ: I concur also.

DR. NAIDU: Ms. Whittington.

MS. WHITTINGTON: I concur.

DR. NAIDU: Ms. Adams.

MS. ADAMS: No additional comments.

DR. NAIDU: Have we answered that question adequately?

MR. MELKERSON: I believe so. Thank you.

DR. NAIDU: Thank you. At this point I would like to thank the panel members for traveling long distances and for all their time that has been put toward this meeting. I would like to adjourn the

meeting at this point.

MR. MELKERSON: Before we adjourn, I would like to thank the speakers who spoke today on this topic. We know it was a difficult topic both for the panel and for the audience as well as for the FDA. Again, we would like to thank the panel members and Dr. Sanjiv Naidu for standing in for Dr. John Kirkpatrick. Thank you.

DR. NAIDU: Thank you.

(Whereupon, at 11:48 a.m. the meeting was adjourned.)